Synthesis of 1,2,4 oxadiazol-5-imine, 1,2,4-triazol-3-imine and derivatives: A Substituted Cyanamide-based Strategy for Heterocycle Synthesis

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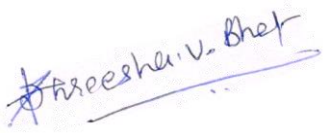
Statement of Originality

"I, Shreesha V. Bhat, hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been published or accepted for the award of any other degree or diploma at University of Lincoln or any other educational institution, except where references have been made in the thesis. Any contribution made to the research by others, with whom I have worked at the University of Lincoln or elsewhere, is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged."



(Shreesha V. Bhat)

Abstract

Considering the importance of nitrogen-rich heterocycles in drug discovery, a novel strategy towards heterocycle synthesis was envisioned using cyanamide chemistry. Synthesis which involve mild conditions, avoids multi-step sequence and non-toxic reagents are desirable for generation of large combinatorial libraries of drug molecules. We envisaged that the NCN linkage of the cyanamide as well as the concomitant use of the nucleo-and electrophilic centres of the cyanamide could provide a novel synthetic route towards nitrogen heterocycles.

The first part (Ch-2) constitute the bulk of the thesis and it focuses on the generation of cyanamide ion and its cyclisative capture with a 1,3-dipole – nitrile oxide *in situ*. The cycloadduct -1,2,4-oxadiazol-5(4*H*)-imine was obtained in good yields, which was further transformed into pharmacologically important cores like oxadiazolone and amidines. A library of the different heterocyclic cores was generated, which tolerated a wide variety of functional groups in good to excellent yields.

In the second part (Ch-3), we developed a novel protocol for the synthesis of 1,2,4-triazol-3-imine *via* a formal 1,3-dipolar cycloaddition of *in situ* generated nitrile imines and cyanamide ion. Further hydrolysis furnished with 1,2,4-triazol-3-one, which is an important core from medicinal chemistry point of view.

The concomitant generation and reaction of two reactive species- 1,3-dipoles and cyanamide ion was achieved in a single pot *in situ* to provide a route towards novel and pharmaceutically important heterocyclic cores. The present work provides a platform for the development of cyanamide derivatives as a 'single-reagent—diverse-scaffolds' strategy for time efficient library delivery of structurally diverse molecules.

Acknowledgment

I am sincerely and heartily grateful to my supervisor, Dr Pallavi Sharma, for her unwavering support and encouragement. Her knowledge, work ethics and wisdom have always inspired and motivated me. I would like to thank her for standing by me through my mistakes and always giving me the chance to improve further. I have been fortunate to receive all the technical training first-hand from her, and I have learnt a lot in terms of carrying out research projects without the inherent biasness and in a time-bound fashion. All the credit for the completion of the PhD in three years goes to her, as she was always there to give inputs and drive the project to completion. Despite my shortcomings, she has always been patient with me and guided me towards the right direction. I would also like to acknowledge the School of life-Sciences and School of Chemistry, University of Lincoln for a fully funded PhD studentship and the utilisation of research instruments and other facilities.

I would also like to thank my lab mates – Dr. Ranga whose company I have always enjoyed. He has been an excellent team-mate to work with and we had some good time in the lab discussing chemistry. I will have to give credit to Abhishek and Anish for maintaining a cheerful lab environment. I will never forget the funny moments we had in the lab. I had developed a great rapport with Anish as we worked late into nights and I have always been amazed by his energy and enthusiasm towards work. I would also like to thank Abhishek for taking the effort to print the final thesis for me. I will always cherish the scientific discussions in the lab with Louis (Dr. Louis Adriaenssens) who has been a great support towards the later part of my PhD. I cannot express my gratitude enough for Martin (Dr. Martin Lear) for his role as the internal evaluator for my MPhil/PhD transfer as well as the PhD viva. I thank him for being so understanding and being patient during the correction process.

Special thanks to Dr. John Moses (University of Nottingham) whose support helped us in running the NMR and mass analysis in the first year of PhD when we didn't have NMR in UoL. I would also like to thank our collaborators - Dr. Robinson (computational studies) and Dr. Stefan (Hsp90 assays). I express my gratitude towards all the technical staff members including Julian, Mathieu, Leonie, Stephen and Elisa for the instrument support, and making sure the instrument is up and running. Special mention must go to Angie who always made sure that we were doing alright in terms of lab resources in JBL. Sincere thanks to all the

technicians including Beverly, Angela, Keith, Dan, Martin, Joel who made our life a lot easier in the lab. I would also like to thank the lecturers I worked with as a GTA including Pallavi, Ruth, Belinda and Jose. Their inputs have helped me in doing my job better.

A big thanks to the school administrators Sharon, Emma and Lynn for their efforts in processing all the necessary forms and other important admin work. A sincere thanks to the security staff at JBL including Gavin, Tony, Les, Peter and the late George who always made sure I was alright while working in the evenings and nights in the second-floor labs.

Some of the nicest people I have come across in Lincoln was in the JBL second floor research office, with people from different nationalities and culture. I had the pleasure of interacting with Paolo, Nabilah, Praew, Aqssa, Rashidi, Sam, Emily, Maxime and Ben who all made the PG life more interesting in Lincoln. Sharing the PhD journey with Mandy, Tammy and Maria was great as we all started our journey at the same time and could share and relate to each other's problems common in everyday PhD life. I wish them all the best in their future endeavours.

Life would not have been so fun without the friends I have made in Lincoln. It was a pleasure being housemates with Payel and Mriganka, who were like family away from home. Most of my trips across UK have been with them, and those memories will always stay with me in my subconsciousness. I met my brother from another mother, Dr. Mohammed, one of the kindest soul I have come across till date. It always felt like I have known him since long, as we made innumerable trips across Brittania (as his daughter would say) all captured on my camera lens. Our conversations about various topics ranging from culture, religion, middle-east politics, food and life were an absolute delight for my curious mind. Hopefully, we will cross paths again in future.

It was a fateful day that I decided to go for a quiz hosted by the graduate school where I teamed up with Anthony, and since then we have been partners in many activities. Right from stealing productive breaks for a game of chess or a snack in the lawn overlooking the architecture building, attending jazz sessions every week or playing pool over weekends, having lunch in the atrium or going on adventurous walking trails, we have been involved in many adrenaline-raising activities which made me cheerful when facing failures in the lab. His enthusiasm towards life and social entrepreneurship has been infectious and awe-inspiring altogether.

Another person who was a constant support for me in Lincoln was Subash, the university chaplain. Apart from the role of chaplaincy in organising various multi-faith events which I was a part of, he has been a dear friend and his home was always open for me. Two people who were important in my journey despite the distances spanning continents were Harshit and Dr. Mohit Tyagi. Harshit has been with me since the past 10 years and our friendship has stood the obstacles of time and distance. Dr. Mohit has been a constant inspiration and has always pushed me in the right direction. His guidance while applying for PhD positions and later during the PhD has been of immense value.

The most challenging time of my PhD studies were the three months of thesis writing. As I went into a shell isolated from the outside world, seeking solace within myself, my decision to go to the student well-being centre helped me in breaking the pattern I had fallen into quite deeply. The accumulated guilt of not having written enough in the first 1.5 months due to procrastination had lead me into a state I would never wish to return to. But, the support I received later from my supervisor and Ranga, was what lifted me up, and made me submit the thesis right near the deadline. I would be always thankful to them for being there for me and providing support during those tough times. A major credit for submitting my final corrections would go to Dr. Dolly Anadkat, who helped me in tackling procrastination after returning to India. A big shout out to Prithvi Cafe (Ahmedabad, India), the place where I spent a month while correcting my thesis. The staff headed by Nepal Singh were very friendly and ever-smiling which kept my spirits high.

Lastly, my heartfelt gratitude goes towards my family who have always offered me every form of support and love at every stage of my life. I could not have asked for a more better upbringing, where my parents always made sure that nothing affected my studies. My mother and father have always encouraged me in my endeavours and I am indebted to them for life. I would like to dedicate this thesis to my parents, the least I could do for them. I also thank my sister, who was my inspiration to pursue science in the first place. I was introduced to the world of drugs by her, which led me to pursue my under-graduate and postgraduate studies in pharmacy and later transitioning to organic chemistry. My last acknowledgement would go to all the scientists whose papers have contributed towards my knowledge and the research described in this thesis. Special mention must go to Prof. Rolf Huisgen, whose meticulous research and inspiring life story kept me motivated throughout my PhD.

Table of Contents

List of abbreviations

CAAC - cyclic (alkyl)(amino) carbene

CNDO/2 – Complete neglect of differential overlap

COSY - Correlation spectroscopy

CuAAC – Copper-catalysed azide-alkyne cycloaddition

d – doublet

dd – doublet of doublet

DCC – *N*, *N*'-Dicyclohexylcarbodiimide

1,2-DCE - 1,2-dichloroethane

DCM – Dichloromethane

DDT - 1,1-bis(p-chlorophenyl)-2,2,2-trichloroethane

DG – Donating group

DIB – (diacetoxyiodo) benzene

DIPEA – Diisopropylethylamine

DMAP – 4-(Dimethylamino) pyridine

DMF - Dimethylformamide

DMSO – Dimethylsulfoxide

DNA – Deoxyribonucleic acid

EDC - 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

EDPBT - 1,2-ethyllenepyridinium bistribromide

EtOAc – Ethyl acetate

ETM – Electronic transmitting material

Equiv. – equivalent

FAD – Flavin-adenine dinucleotide

FMO – Frontier Molecular Orbital

HOMO – Higher occupied molecular orbital

HMBC - Heteronuclear multiple-bond correlation spectroscopy

HMQC - Heteronuclear multiple quantum coherence

Hsp90 – Heat shock protein 90

GC-MS- Gas chromatography-Mass spectrometry

HRMS (ESI) - High resolution mass spectroscopy electrospray ionisation

HSQC - Heteronuclear single-quantum correlation spectroscopy

IR – Infra-red

IUPAC – International union of pure and applied chemistry

LCMS - Liquid chromatography mass spectroscopy

LUMO – Lowest unoccupied molecular orbital

MCR – Multicomponent reaction

MHz - Megahertz

Mol - molar

mp - melting point

m - multiplet

µW/ MW - microwave irradiation

ORTEP – Oak Ridge Thermal Ellipsoid Plot

NAD – Nicotinamide-adenine dinucleotide

NCS - *N*-Chlorosuccinimide

NCTS - *N*-cyano *N*-phenyl-*p*-toluenesulfonamide

NHC – *N*-Heterocyclic carbene

NMR - Nuclear magnetic resonance

OLED - Organic light emitting diode

Pet Ether – Petroleum ether

PPAR – Peroxisome proliferator-activated receptor

Ppm – Parts per million

Py – pyridine

RCM – Ring closing metathesis

R_f - Retention factor

RuAAC – Ruthenium-catalysed azide-alkyne cycloaddition

s - singlet

S_N2 –substitution nucleophilic (bimolecular)

SOMO - Single occupied molecular orbital

t - triplet

TBAF - Tetrabutylammonium fluoride

TEA -Triethylamine

Temp - Temperature

THF – Tetrahydrofuran

TMEDA - *N*, *N*', *N*', *N*'- Tetramethylenediamine

TMS - Tetramethylsilane

TMSCN - Trimethylsilylcyanide

TNT - Trinitrotoluene

TLC - Thin layer chromatography

TPPO – Triphenylphosphine oxide

Ts - Tosyl

US-FDA – United States Food and Drug Administration

To My Mummy and Papa

(who are an epitome of love and selflessness)

To My Sister

(who has been a constant inspiration)

And

To Science

(which has been and always will be an integral part of my life)

"Stubborn pursuit of a goal is often praised as a virtue, and sometimes leads to success. However, accidental observations can disclose new horizons, far off the original target and sometimes more valuable. The luck chance might lurk just outside the experimenter's door, but the door is not always open. Opening it brings serendipity – acceptance of Fortuna's gift."

"The solution of one problem usually generates a bevy of new ones. The inexperienced young scientist often lacks the willpower to resist the temptation of dealing with a new problem while working on the first one."

"Playfulness is an incentive for the scientist and a driving force of progress"

-Rolf Huisgen

(in his autobiography – 'The Adventure Playground of Mechanisms and Novel Reactions')

Chapter-1

Introduction to Heterocycles and Cyanamides

Chapter 1

Introduction to Heterocycles and Cyanamides

1.1 Heterocycles

The IUPAC Gold Book describes heterocyclic compounds as: '*Cyclic compounds having as ring members atoms of at least two different elements, e.g. quinoline, 1,2-thiazole, bicyclo[3.3.1]tetrasiloxane'*.[1]

Another classical reference book, the Encyclopaedia Britannica, describes a heterocyclic compound as: *'Any of a major class of organic chemical compounds characterized by the fact that some or all of the atoms in their molecules are joined in rings containing at least one atom of an element other than carbon (C), most frequently oxygen, nitrogen, or sulfur*'.[2] However, many other atoms can form the stable covalent bonds necessary for ring construction including phosphorus, arsenic, antimony, silicon, selenium, tellurium, boron, and germanium.[3]

Heterocyclic compounds are commonly found as 3 to 8 membered rings, although five and six-membered rings are more prominent in nature.[4] The five-membered heterocycles studied generally include ─ containing (i) one-heteroatom (pyrrole, furan, thiophene), (ii) two-heteroatoms (pyrazole, imidazole, oxazole, thiazole) (iii) three-heteroatoms (oxadiazole, triazole, tetrazole) (Figure 1.1). Fused heterocycles like indole, benzimidazole, benzoxazole, indoles etc. are also widely distributed/studied.[5]

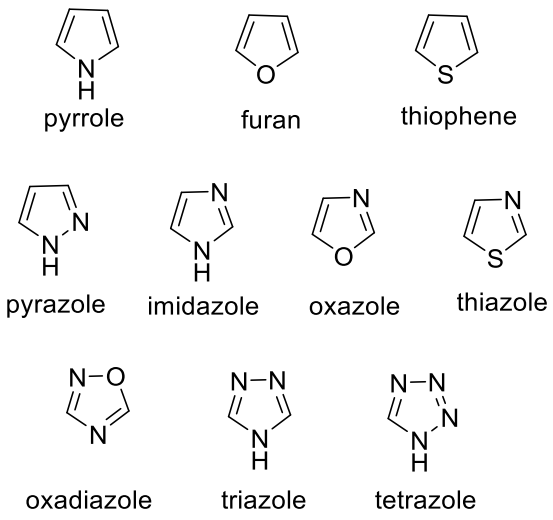


Figure 1.1 Some common five-membered heterocycles

Around 133,326 different heterocyclic ring systems had been reported upto 1984,[4] with many more being added since then. Moreover, with possibility to decorate these core ring systems *via* substitution with different functionalities, millions of heterocyclic compounds have been synthesised till date. A recent analysis of the organic compounds registered in *Chemical Abstracts* revealed that as of June 2007, there were 24,282,284 compounds containing cyclic structures, with heterocyclic systems making up many of these compounds.[6] As Rolf Huisgen had said, *'The number of organic compounds is potentially infinite. Nowhere does one feel confronted with this profusion to a higher extent than in heterocyclic chemistry'*,[7] highlighting the increasing role of heterocyclic molecules in organic chemicals.

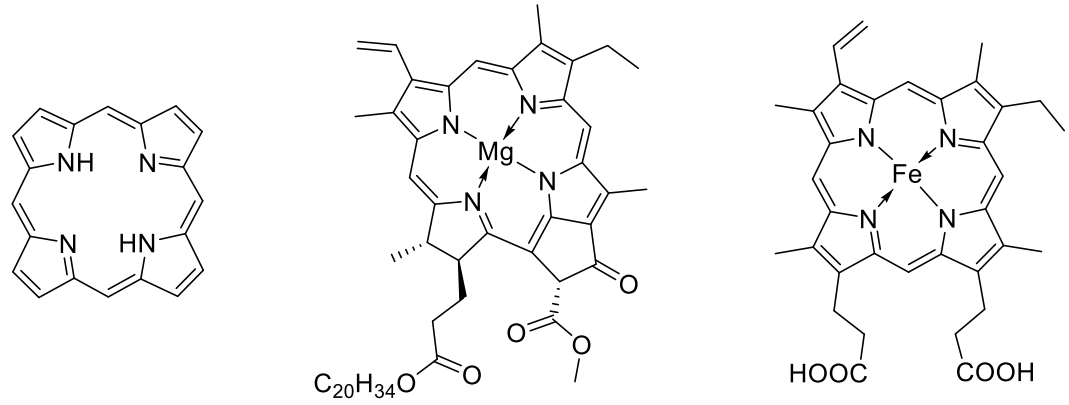
The history of heterocyclic chemistry can be dated back to 1800s, in step with the development of organic chemistry.[8] The early heterocyclic compounds were mostly isolated from natural resources, some of the notable historic examples being:

- Uric acid (1776, by Scheele from human bladder stones),
- Alloxan (1818, by Brugnatelli on oxidation of uric acid),
- Quinoline and Pyrrole (1834, by Runge from coal distillates, called coal tar),
- Melamine (1834, by Liebig by synthesis),
- Pyridine (1849, by Anderson by pyrolysis of bones),
- Indole (1866, by Baeyer from degradation of indigo, synthesised by Friedlander in 1906),
- Furan (1870, from wood and cellulose destructive distillation)
- Chlorophyll (1936, isolation by Treibs)

The plant kingdom forms a rich source of many nitrogen heterocyclic compounds, most common being the alkaloids (alkali in nature). Natural products like morphine, quinine, camptothecin, vinblastine nicotine, reserpine are some of the important alkaloids isolated from plant sources.[9]

Porphins (four pyrrole units linked in a cycle by four sp^2 carbons) and their derivatives known as porphyrins are an important class of natural heterocyclic molecules, which play an important role in the respiratory system of both plants and animals. Two of the most important porphyrins include- the iron (II) complex heme which when associated with the protein globin is found in blood as the oxygen-carrying hemoglobin, and chlorophyll, which is a magnesium complex

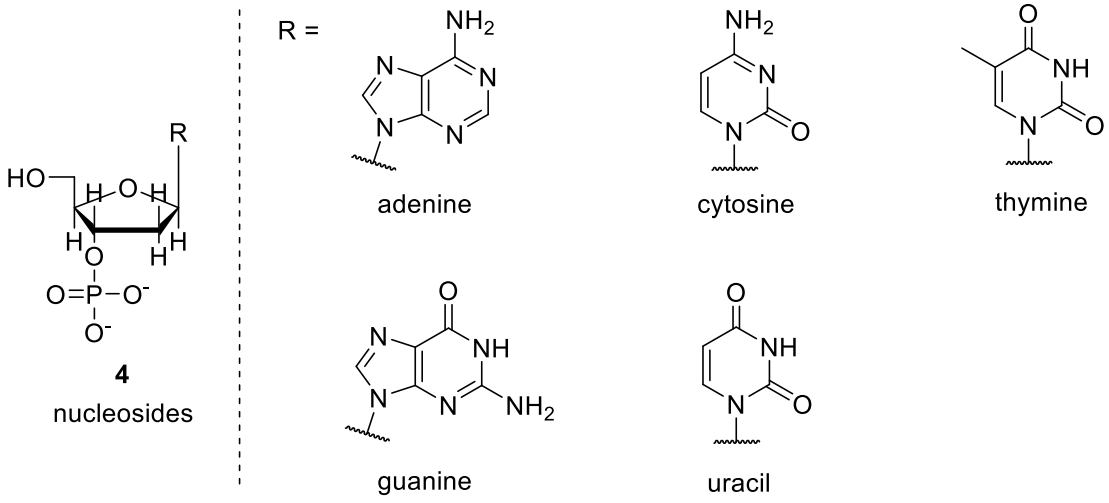
involved in photosynthesis (Figure 1.2). One of the vitamins (B12, cyanocobalamine) also contains a modified porphin ring, which is complexed to cobalt.



1 porphin **2** chlorophyll-a **3** heme

Figure 1.2 Porphyrin containing natural molecules: chlorophyll-a and heme

The genetic material DNA, the basis of life comprising of nucleic acids (**4**) having heterocyclic bases – pyrimidines: cytosine, thymine and uracil and purines: adenine and guanine are important building blocks of life (Figure 1.3).[9]



4 nucleosides

Figure 1.3 Nucleic acids with purine and pyrimidine heterocycles

Examples of heterocyclic core also appear in several amino acids and neurotransmitters. For example, the essential amino acids: proline (**5**, pyrrolidine), tryptophan (**6**, indole), histidine (**7**, imidazole) are important amino acids in life, whereas the neurotransmitters serotonin and histamine are important in the modulation of the body's and biochemical processes; whereas melatonin (**10**) is involved in the regulation of circadian rhythms (sleep patterns).

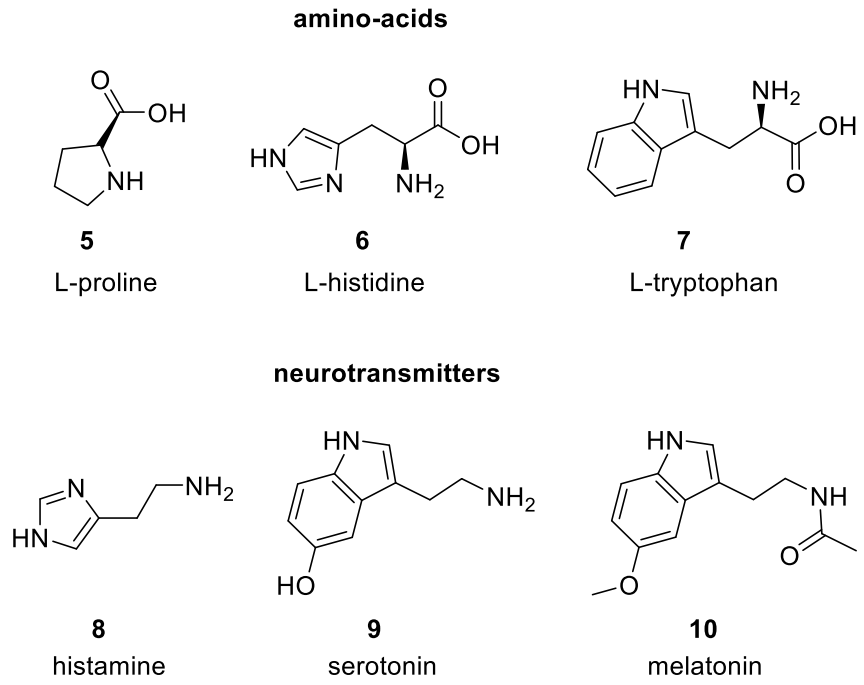


Figure 1.4 Heterocyclic structures found in amino acids and neurotransmitters

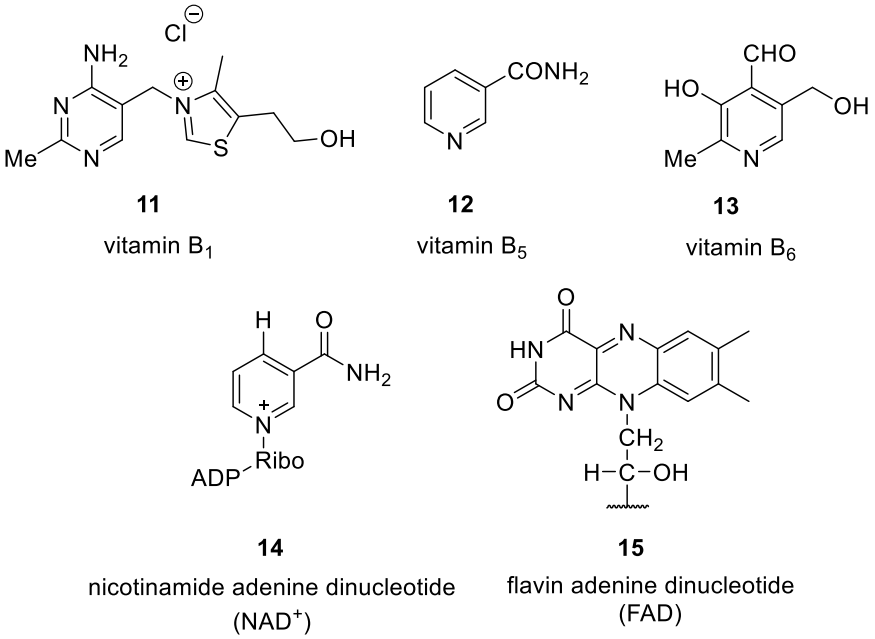


Figure 1.5 Heterocycles found in vitamins and cofactors

Heterocyclic molecules are also important constituents of vitamins, co-enzymes and antibiotics. Thiazolium ring is prominent in vitamin B_1 (**11**), and its co-enzyme form plays an important role in the decarboxylation of α-keto-acids. Vitamin B_5 (**12**, nicotinic acid amide)

and Vitamin B_6 (**13**, pyridoxal) are pyridine-based molecules, whereas the co-enzymes NAD (**14**) and FAD (**15**) are important biochemical catalysts for the physiological processes in the body (Figure 1.5).

1.2 Heterocycles in Drug Discovery

Heterocycles are common structural scaffolds in marketed drugs and in medicinal chemistry targets in the drug discovery process. Over 80% of top small molecule drugs by US retail sales in 2010 contained at least one heterocyclic fragment in their structures.[10] In fact, heterocyclic moieties are present in the structures of all top 10 brand name small molecule drugs.[10] The importance of nitrogen containing heterocycles can be estimated from the fact that approximately 60% of all unique small molecule drugs approved by US-FDA contain at least one nitrogen atom.[11]

One of the reasons for the widespread use of heterocyclic compounds is that their structures can be subtly manipulated to achieve a required modification in function. Some of the drug properties that can be modulated by a strategic inclusion of heterocyclic moiety into the molecule include: 1) potency and selectivity through bioisosteric replacements, 2) lipophilicity, 3) polarity, and 4) aqueous solubility.[10]

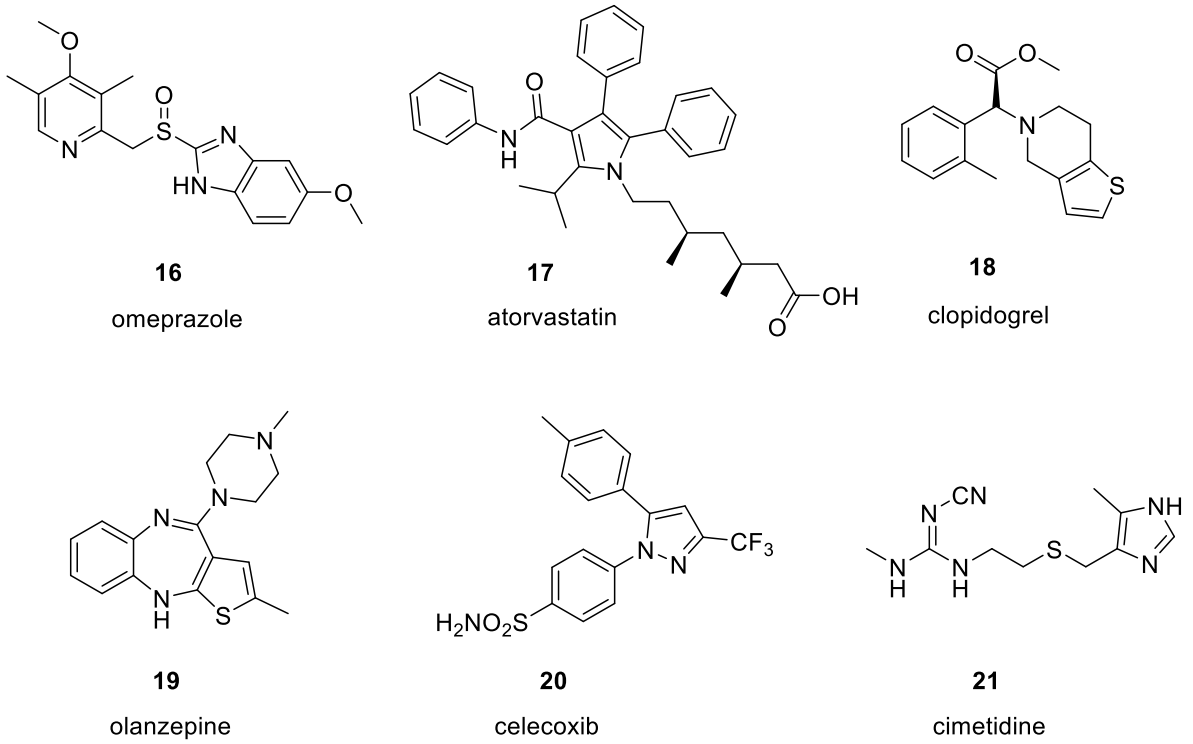
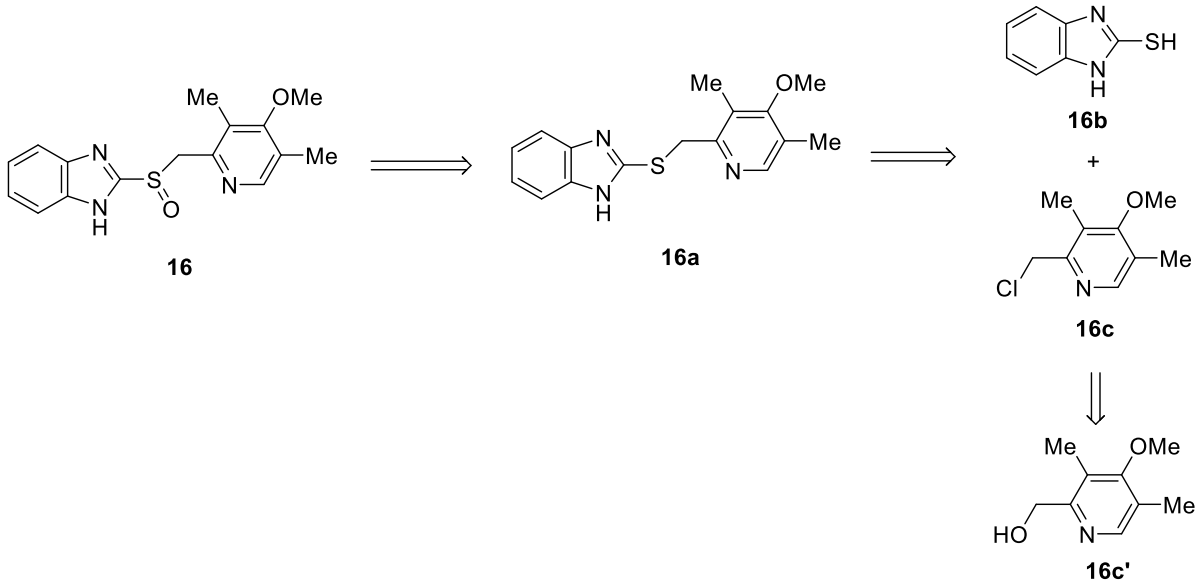


Figure 1.6 Some top-selling drugs containing heterocyclic cores

Heterocyclic groups acts as bioisosteres for different functional groups, for example the use of tetrazole ring system is used as a mimic of a carboxylic acid functional group[12] as it is similar in terms of acidity and steric requirement. The tetrazole group is found to be superior in terms of metabolic stability, bioavailability and greater charge distribution.[12]

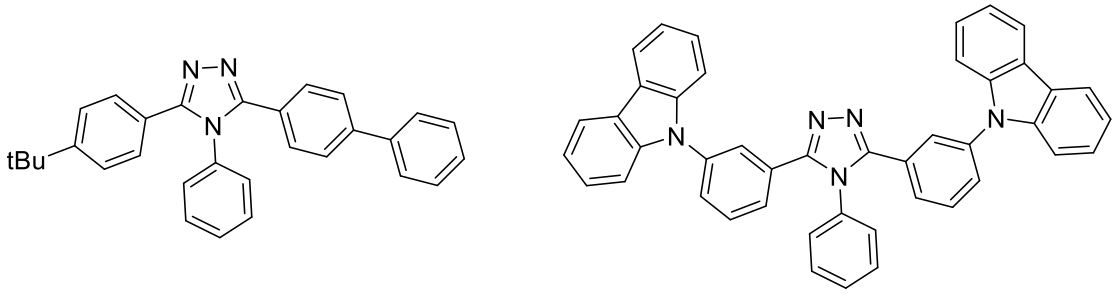


Scheme 1.1 Retrosynthetic scheme for omeprazole

One of the important biological interactions involve the hydrogen bonding of the drugs with the target proteins, which can be achieved via heterocyclic rings. [13] They also provide good chelation properties (for e g. the binding of the heterocyclic component of the HIV-1 integrase inhibitor Raltegravir to Mg^{2+} and Mn^{2+} which are important cofactors of the integrase enzyme provides its activity).[14] Heterocycles are also used to reduce the lipophilicity of the drug compounds, as they contain lower ClogP values. In addition, they can modulate the polarity and aqueous solubility of compounds, hence playing an important role in the drug discovery process. Several drugs known in the market contain a nitrogen heterocycle.[9] Some of the top-selling drugs[15] including atorvastatin (cholesterol-lowering), omeprazole, clopidogrel, olanzapine, celecoxib and cimetidine are illustrated in Figure 1.6. The retrosynthetic analysis of omeprazole is shown in Scheme 1.1. 2-thiobenzimidazole (**16b**) and 4-methoxy-3,5-dimethyl-2-chloromethyl pyridine (**16c**) react to give **16a** which when oxidized gives omeprazole (**16**).

1.3 Heterocycles in Materials chemistry

Heterocylces also find application in material science and have been widely used for constructing polymeric material,[16] and smart materials. In particular the 5-membered and 6-membered nitrogen heterocycles have been recently explored as an efficient light emitting source and have also been used to build high performance electron-transport materials (ETMs) with high electron mobilities, high triplet energy levels and low electron injunction barriers.[17,18] OLEDs (Organic light emitting diodes) have become one of the most sought after research area in the light-emission field, due to their potential applications in flat panel displays, solid-state lighting, and back-lighting sources for liquid display.[19]



22 **23**

Central ring - 1,2,4 -oxadiazole, 1,3,4-oxadiazole or 1,2,4-triazole

Figure 1.7 Heterocyclic molecules in light emitting materials[20]

Among the 5-membered *N*-heterocycles, due to electron-deficient nature of the 1,2,4-oxadiazoles, 1,3,4 oxadiazoles and 1,2,4-triazole rings, their use as an electron transport layer and hole-blocking material in multi-layer type electroluminescent cells has been demonstrated[17,18,20,21] (Figure 1.7). Heterocyclic molecules have also found application in liquid crystals which finds applications in displays, optoelectronic devices and as sensors due to their special properties (Figure 1.8).[17] Heterocycles on alkylation find use as ionic liquids which aggregate electrostatically. Imidazolium salts in particular are used to extract metal ions from aqueous solutions, dissolve carbohydrates, create polyelectrolyte brushes on surface, coat metal nanoparticles and create oriented liquid crystals.[22]

Polymers of nitrogen heterocyles like 1,2,4-triazole and 1,2,4-oxadiazole have found use in data storage, electrolyte membrane fuel cells and solar cells. Pyrrole-imidazole polyamides have been used as sequence-selective DNA probes and their conjugation with fluorophores have found application in biological imaging.[23,24] Imidazole and imidazolium based polymers

form hydrogels- a form of responsive polymer which swells nearly 200 times the original volume and found applications in drug release, sensors and artificial muscles.[22]

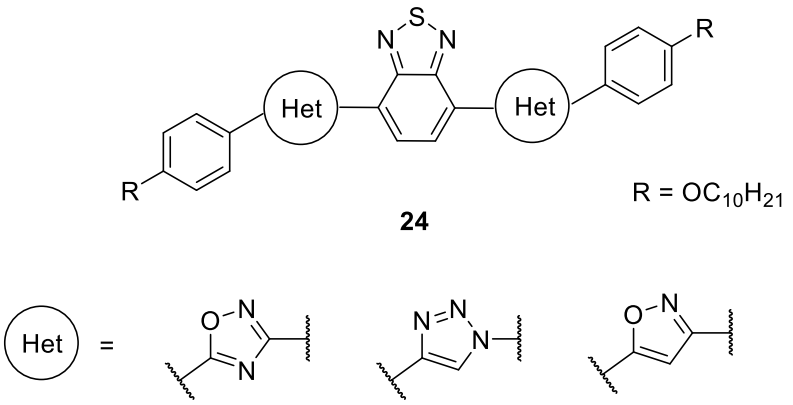


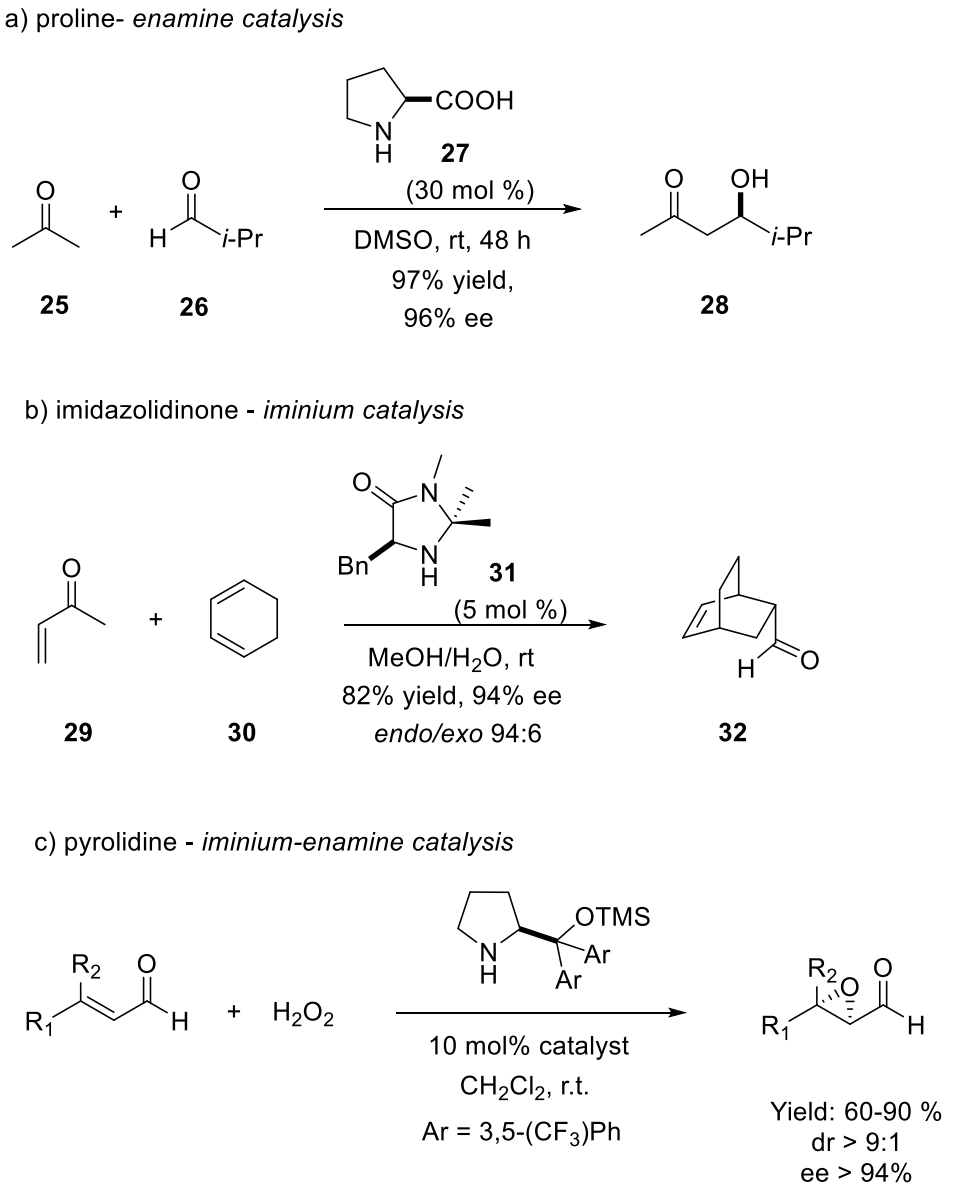
Figure 1.8 Benzothiadiazole-based liquid crystal containing different heterocyclic substituents[17]

1.4 Heterocycles in Catalysis

In early 2000s Berber and Macmillan introduced heterocycles like proline and imidazolidinone as organocatalysts for various asymmetric transformations. Organocatalysts have advantages over traditional metal-based chiral catalysts[25] – a) generally insensitive to oxygen and moisture in the atmosphere, thus avoiding the need for special reaction vessels or ultra-dry reagents and solvents; b) non-toxic and environment friendly; c) easy availability from natural sources as single enantiomers, hence making it cheap to prepare in large quantities.

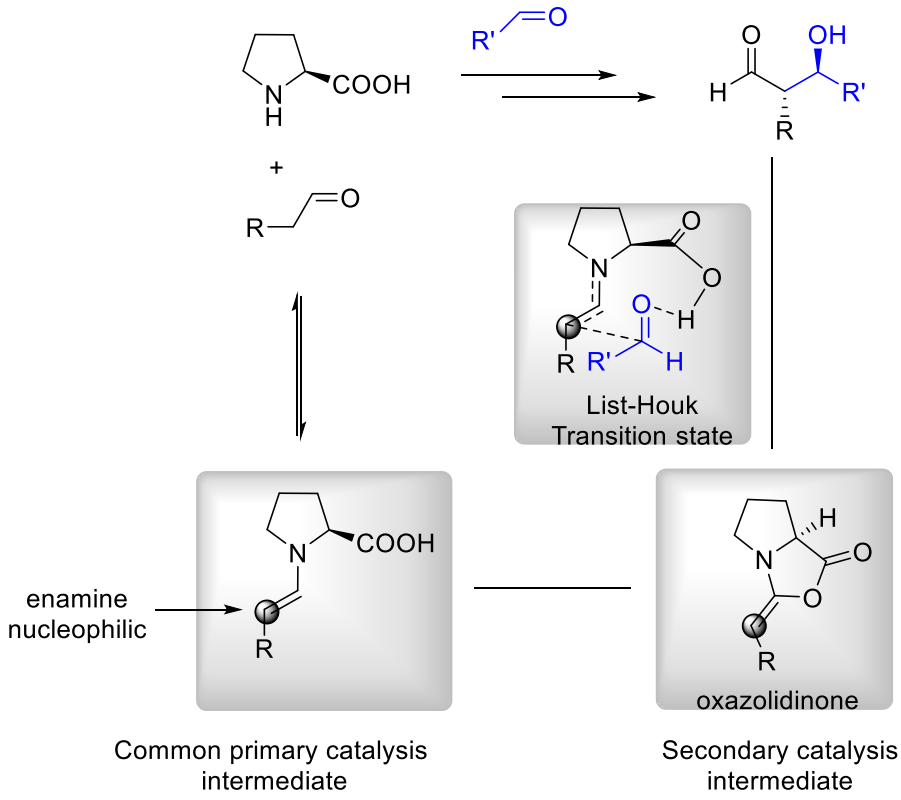
Organocatalysis has its basis on 5-6 different generic activation modes, and its classification has evolved since its discovery. Different activation modes like – iminium catalysis, enamine catalysis, SOMO (single occupied molecular orbitals) and counter anion catalysis operate on covalent interactions, whereas activation modes like hydrogen bonding, phase transfer catalysis and Bronsted acid involve non-covalent interactions.

One of the early examples of proline-catalysed reaction was the inter-molecular cross aldol reaction,[26] where the proline (**27**) formed a nucleophilic enamine on condensation with an aldehyde (**26**) and reacted with a ketone (**25**) to form a cross aldol product (**28**) in good yields (Scheme 1.2a).



Scheme 1.2 Reactions catalysed by proline and imidazolidinone-based organocatalysts

Enamine catalysis is considered bifunctional catalysis, as the amine-containing catalyst (proline) reacts with ketone to form a nucleophilic enamine, and simultaneously engages with an electrophilic reaction partner through either hydrogen bonding or electrostatic interaction.[27] (Scheme 1.3). The products are formed through α-functionalisation of carbonyl compounds and involves HOMO activation. The enamine intermediate as the primary catalytic species was identified recently by NMR and X-ray spectroscopy[28] in 2010, which also revealed the secondary catalytic species: an oxazolidinone acting as a bridge between aldehyde and enamine (Scheme 1.3).



Scheme 1.3 Mechanistic scheme for aldol reaction – evidence of primary and secondary intermediates

Iminium catalysis was the first organocatalytic activation mode to be designed and used as a general strategy for asymmetric organic synthesis.[25] They are applicable for transformations traditionally catalysed by lewis acids expected to emulate equilibrium dynamics and π-orbital electronics inherent to Lewis acid catalysis (lowering activation energy of LUMO). Condensation of a chiral secondary amine with an enal forms the iminium ion, the LUMO orbital of which is lowered in energy such that it can now interact with suitable coupling partners through either pericyclic reactions or by conjugate addition[26] (Scheme 1.2b and 1.2c).

The first highly enantioselective organocatalytic Diels–Alder reaction using a chiral organocatalyst was reported by Macmillan in 2000.[29] The activated iminium ion, formed through condensation of the imidazolidinone (**31**) and an α,β-unsaturated aldehyde, reacted with various dienes to give [4+2] cycloadducts in excellent yields and enantioselectivities (Scheme 1.2b). The dimethyl substitution of the imidazolidinone catalyst keeps the bulk of the iminium ion in a position so as to form a π-π stacking of the benzyl group with alkene unit, blocking the top face of the alkene and leading to a high facial selectivity.

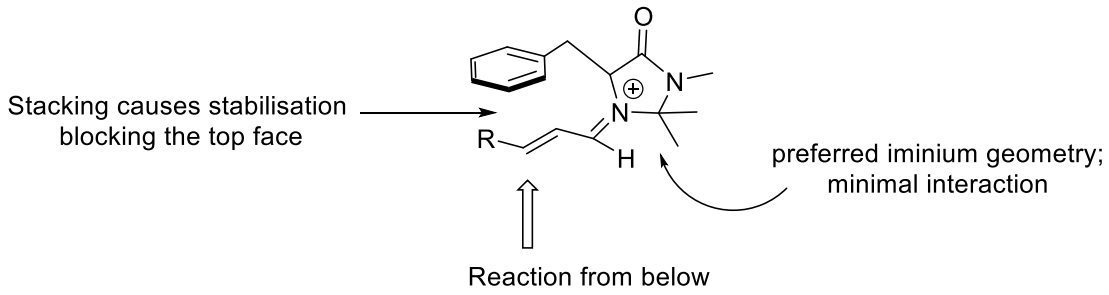
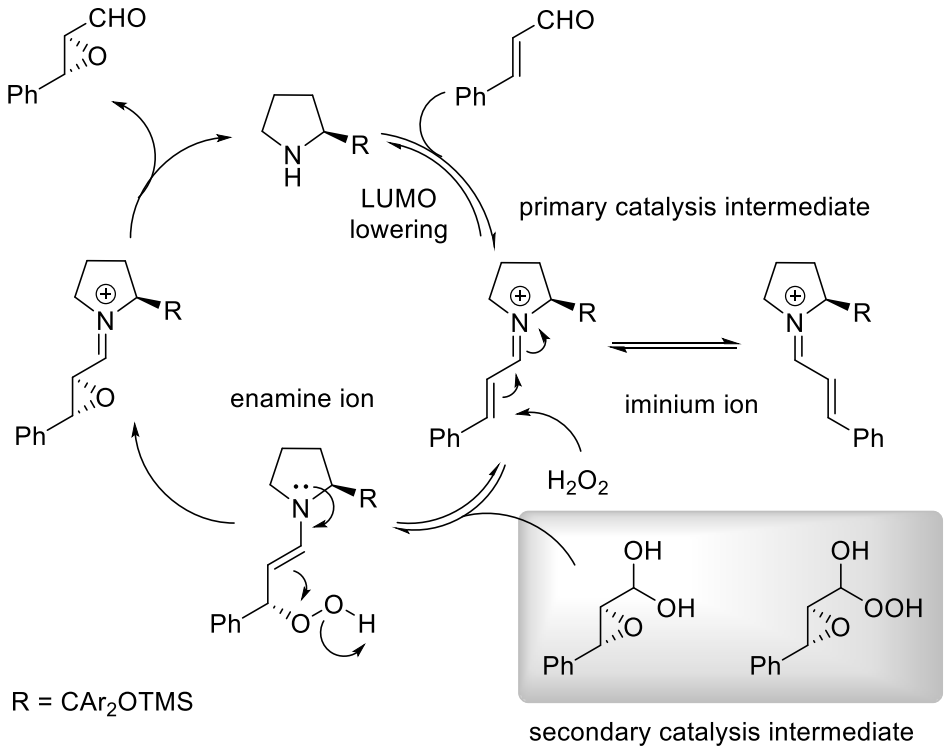


Figure 1.9 Orientation of imidazolidinone catalyst responsible for enantioselectivity

Another example of an iminium-enamine catalysis is the Jorgensen epoxidation of α,β-unsaturated aldehydes by hydrogen peroxide catalysed by diarylprolinol derivative.[30] (Scheme 1.2c). The first step is the formation of the iminium ion intermediate by reaction of the α,β-unsaturated aldehyde with the chiral amine. In the next step, the peroxide adds as a nucleophile to the electrophilic α-carbon atom leading to an enamine intermediate. The formation of the epoxide then takes place by attack of the nucleophilic enamine carbon atom to the electrophilic peroxygen atom, followed by hydrolysis of the iminium intermediate.



Scheme 1.4 Mechanism of the Jorgensen epoxidation of α,β-unsaturated aldehydes

While it goes through the enamine/iminium intermediate route, the secondary intermediate peroxyhydrate has been implicated in accelerating of the reaction by functioning as a phase transfer catalyst. Similar to the methyl groups in imidazolidinone, it was found that the silyl

group in the prolinol derivative was responsible for the enantioselectivity by discriminating between the two planar faces of the electrophile.[31] Other organocatalytic transformations such as 1,3-dipolar cycloadditions, Friedel–Crafts alkylations, α-chlorinations, α-fluorinations, and intramolecular Michael reactions have been carried out using these catalysts.[26]

Heterocyclic molecules has also been explored as chelating ligand with transition metals which in turn act as catalysts for a variety of reactions.[32–35]Among these, *N*-heterocyclic carbenes (NHC) derived from imidazole, pyrazole and triazole have found use as ligands for metals, their complexation and coordination chemistry being very similar to organophosphanes.[36,37] They are σ bond donors and bind strongly to the metals. They have been found to be versatile in their applications e g. palladium-NHC complexes have found use as catalysts in Heck, Stille, Sonagashira coupling, aryl amination, etc.[38–41] Although considered 'phosphine-mimics' there have been increasing evidence that NHC─metal catalysts surpass their phosphane congeners in both activity and scope of application.[42] The most convincing and best studied example so far has been olefin metathesis, for which ruthenium-NHC catalysts were exploited. It was found that the organophosphanes─ubiquitous standard ligands in organometallic chemistry gave poorer catalytic performance than NHC ligands in structurally analogous catalysts. The NHC-ruthenium complexes gave rise to the second generation Grubb's catalyst. Further replacement of a phosphine ligand from the second generation Grubb's catalyst with a heterocyclic molecule like pyridine led to a million-fold increase in the initiation rate.[43] This fast-initiating catalyst has found use as initiators for ring opening metathesis polymerisation (ROMP),[44] and are called third-generation Grubb's catalyst.[43,45]

1.5 Heterocycles in Pesticides and Agrochemicals

Ever since the discovery of synthetic agrochemicals in the late 1940s like DDT - 1,1-bis(p-chlorophenyl)-2,2,2-trichloroethane) and parathion as powerful insecticides, many synthetic compounds were found to be of commercial values, heterocycles being prominent among them. Various 5- and 6─membered heterocyclic ring containing molecules were discovered as effective insecticides, fungicides as well as herbicides[8] (Figure 1.9). They act through inhibition of various target enzymes/ion channels leading to their pesticidal activity, for eg. The insecticide fipronil (**38**) which is a pyrazole derivative, acts by disrupting the central nervous system of the insects, specifically by blocking chloride ion passage in the system. Some representative examples are found in Figure 1.10.

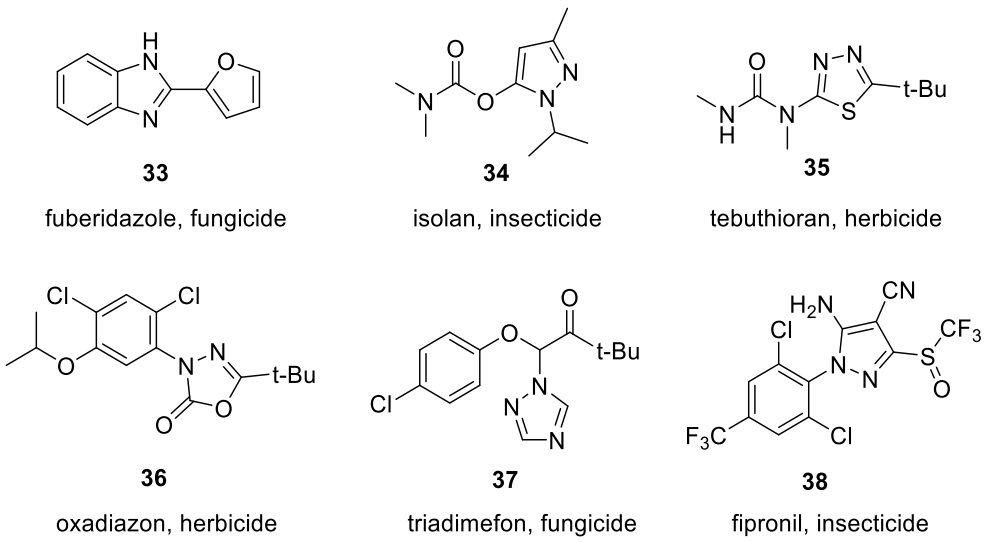


Figure 1.10 Five-membered heterocyclic molecules in pesticides

1.6 Heterocycle Synthesis

The synthesis of the most commonly studied 5- and 6- membered heterocyclic rings could be broadly divided into two major categories:[8,46]

- Intramolecular cyclisation
- Cycloaddition reactions

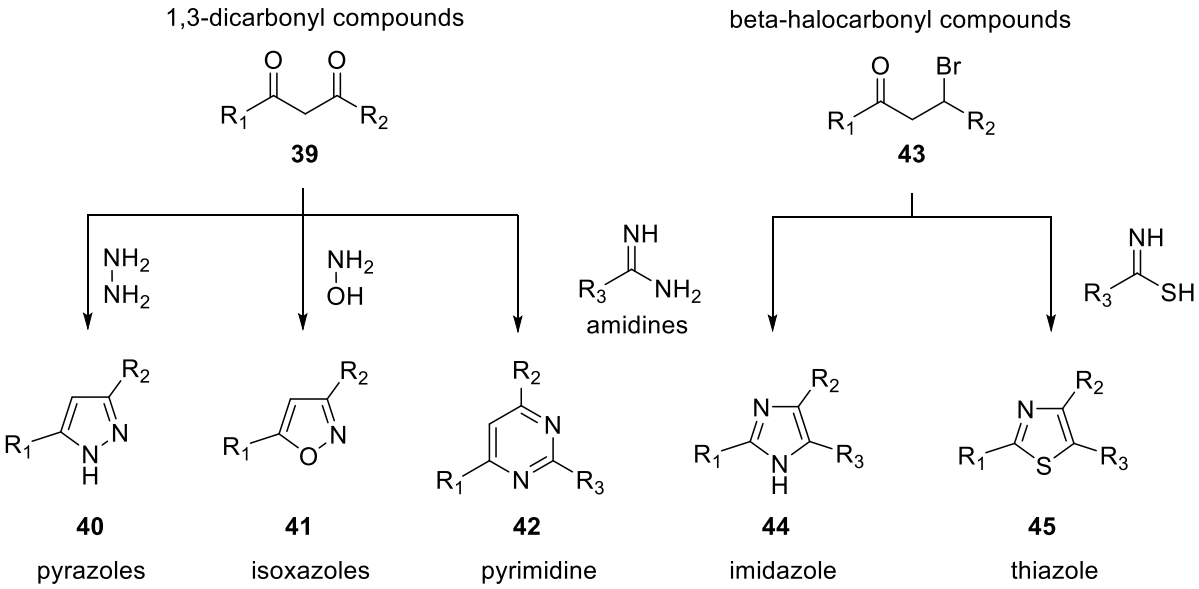
1.6.1 Synthesis of heterocycles by intramolecular cyclisation:

Intramolecular cyclisations involving carbonyl groups, aza-wittig reactions, C-C coupling are some of the commonly employed routes towards heterocycle synthesis.

Carbonyl group condensations:

The primary knowledge that the carbonyl groups in aldehydes and ketones are electrophilic and receptive to addition of nucleophiles like substituted amines, water, alcohols and thiols has led to the synthetic route towards a large number of five and six-membered heterocyclic rings like pyrroles, thiophene, furan, pyridazones, etc.[8]

Heterocycles with two heteroatoms can be synthesised from 1,3-dicarbonyl and β-halocarbonyl compounds by its reaction with different nitrogen nucleophiles (Scheme 1.5). The nucleophilic attack of hydrazine, hydroxylamine or amidine on 1,3-diketone (**39**) leads to the formation of pyrazoles (**40**), isoxazoles (**41**) and pyrimidine (**42**) rings respectively. Similarly, the reaction of β-bromoketone (**43**) with amidine and thioamide generates imidazole (**44**) and thiazole (**45**) ring respectively (Scheme 1.5).[46]



Scheme 1.5 Synthesis of heterocycles by carbonyl condensation

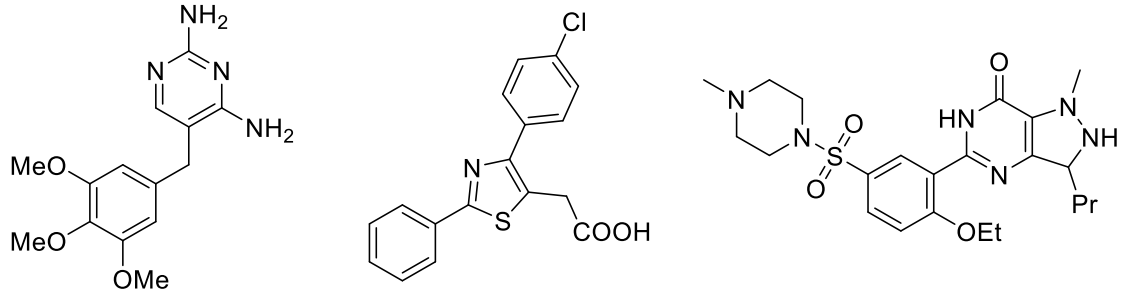
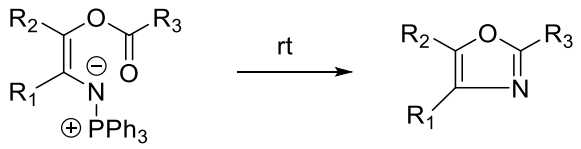


Figure 1.11 Some heterocycle containing drugs synthesised through a key carbonyl condensation step

Intramolecular aza-wittig reaction:

The traditional Wittig reaction involves the reaction of ylides (carbanionic structures stabilised by positively charged phosphonium ion) with carbonyl compounds to form the C-C double bonds. An aza-wittig reaction involves the replacement of carbanionic center with a nitrogen anion forming an iminophosporane, which when reacted with the carbonyl compound forms the C=N bond. Intramolecular aza-Wittig process has been adapted to form a great variety of heterocyclic compounds.[47] A chain containing ester/amide carbonyl groups and iminophosporane at the terminal ends give rise to heterocyclic rings like 1,3-oxazoles (**50**,

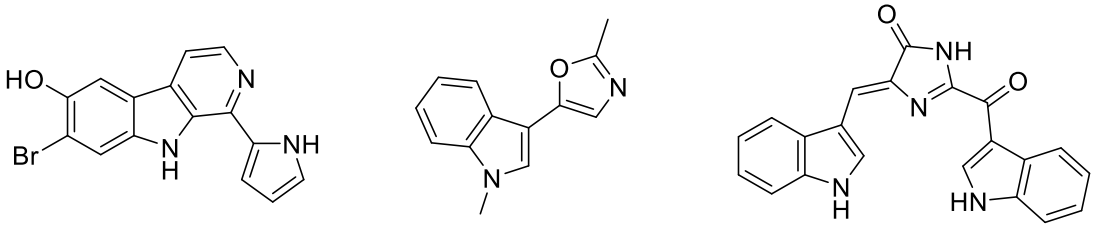
Scheme 1.6), isoquinolines, quinazolines, diazepin-2-ones among others. A large number of natural compounds[48,49] have been synthesised till date, which involve aza-Wittig reaction as the key step (Figure 1.12).



49 **50**

1,3-oxazoles

Scheme 1.6 Synthesis of 1,3-oxazoles by aza-Wittig intramolecular reaction



51 **52** **53**

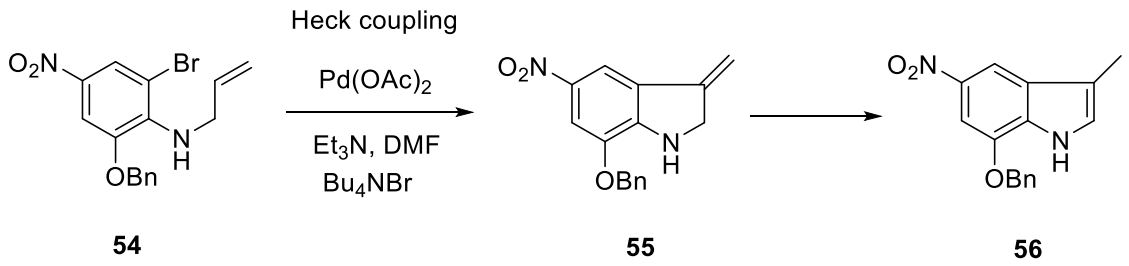
eudistomin A pimprinine rhoapaldin D

Figure 1.12 Natural products synthesised using aza-Wittig reactions as the key step[49]

Cyclisations involving C-C bond formations:

The intramolecular C-C coupling reactions (eg. Heck, Suzuki, Stille reactions) catalysed by transition metals have found applications in synthesis of heterocycles.[50] One of the examples include the synthesis of indole by Heck intramolecular coupling of an olefinic group and halide catalysed by Palladium diacetate. The synthesis by Sundberg[51] proceeded at room temperature to give the product (**56**) in 96% yield (Scheme 1.7).

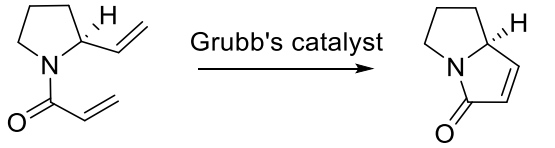
Similar transition metal-catalysed intramolecular reactions of C-C unsaturated compounds tethered with NH, OH, C=O and C=N groups are known to form a wide range of heterocyclic rings. Alkenes, allenes and alkynes have been utilised as carbon-carbon unsaturated compound, and a wide variety of transition-metal complexes, such as palladium, platinum, gold, copper, titanium, tungsten, and organolanthanides have been used as catalysts.[50]



54 **55** **56**

Scheme 1.7 Synthesis of indole ring by intramolecular Heck-coupling

Ring-closing metathesis (RCM) involving an intramolecular interaction between two alkene groups has recently found application in the formation of 5- and 6-membered heterocyclic rings, mainly in the total synthesis of natural products.[50] One of the examples include the synthesis of a pyrrolizidine alkaloid, pyrrolam A[52] (**58**, Scheme 1.8).



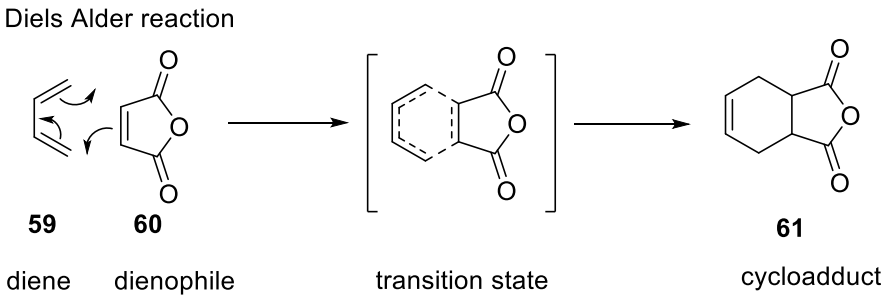
57 **58**
Pyrrolam A

Scheme 1.8 Synthesis of Pyrrolam A by ring closing metathesis (RCM)

1.6.2 Synthesis of Heterocycles by Cycloaddition

The reactions in which *"two or more unsaturated molecules (2 π electron systems) combine with the formation of a cyclic adduct (2 new σ bonds and two less π bonds) can be considered a cycloaddition reaction."*[53] Cycloaddition reactions can be classified according to the number of π components (denoted in brackets) involved in the two reacting molecules: for eg. [4+2] cycloaddition involving 4 and 2 π component systems in the form of diene and dienophile to form a 6-membered ring, more commonly called as Diels-Alder reaction (Scheme 1.9). Similarly, [3+2] and [2+2+1] cycloaddition form 5 membered rings, [2+2] cycloaddition forming four-membered rings, and other higher order cycloadditions like [5+2], [4+3], [4+4], [6+2], [6+4] to form large-membered heterocyclic molecules.[54]

The transition state of the Diels-Alder reaction has delocalised 6 π-electrons, giving it an aromatic character leading to a stable cycloadduct (Scheme 1.9). Figure 1.13 depicts the energy level diagram and the frontier molecular orbital (FMO) interactions of the diene and dienophile (lactic anhydride).[53]



Scheme 1.9 [4+2] Diels-Alder cycloaddition reaction

The HOMO (Highest occupied molecular orbital) of the diene has one node in the center leading to a matching symmetry with the LUMO (Lowest unoccupied molecular orbital) of the dienophile. Dienes react readily with electrophiles because their HOMOs are relatively high in energy. Dienophiles having electron withdrawing groups like carbonyl or nitro lower their LUMO energy leading to better overlap in the transition state with the higher lying diene HOMO. The most common cycloaddition observed thus, is between an electron rich diene (High HOMO) and electron-deficient dienophile (low LUMO)[55] (Figure 1.14)

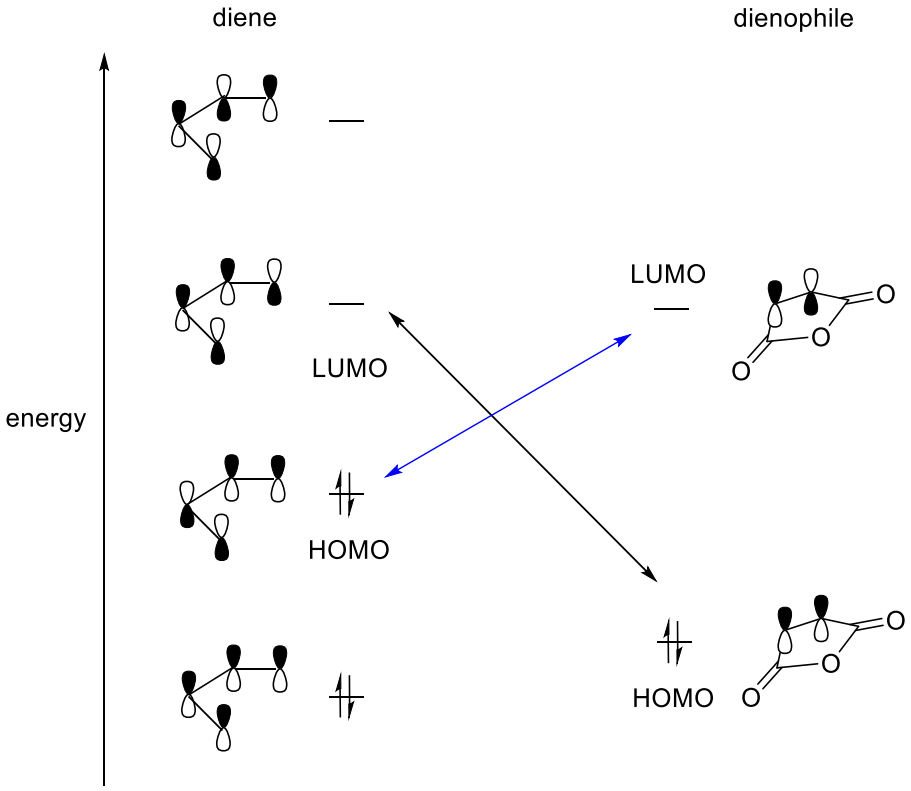


Figure 1.13 FMO of Diels-Alder cycloaddition of diene and cyclic anhydride

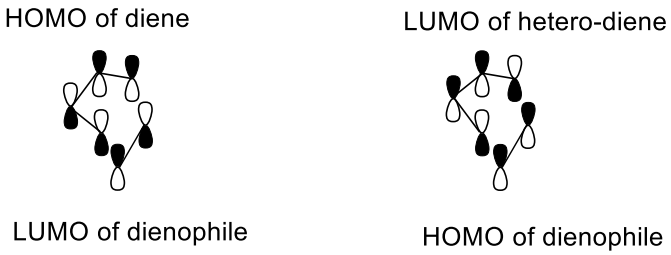
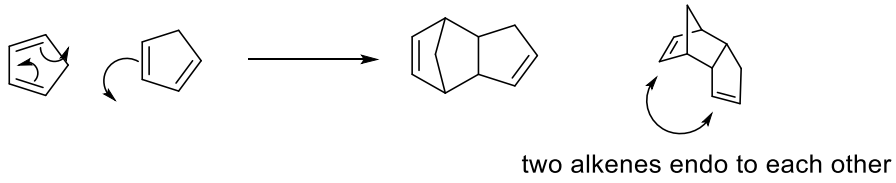


Figure 1.14 Orbital overlap of FMO of diene and dienophile



Scheme 1.10 Dimerization of cyclopentadiene leading to *endo* product

In a Diels-Alder cycloaddition, *exo* product is more stable, but the kinetic *endo* product is formed preferably (Scheme 1.10). Apart from the frontier orbitals interaction, the bonding interaction at the back of the dienes (shown by red arrows, figure 1.15) forming the π-bond leads to lowering of the transition state energy, and makes the formation of the *endo* product more favourable. In case of dienophiles with electron withdrawing groups (eg. carbonyl), a bonding interaction between the carbonyl groups and the developing π-bond at the back of the diene, lowers the energy of transition state leading to *endo* product.

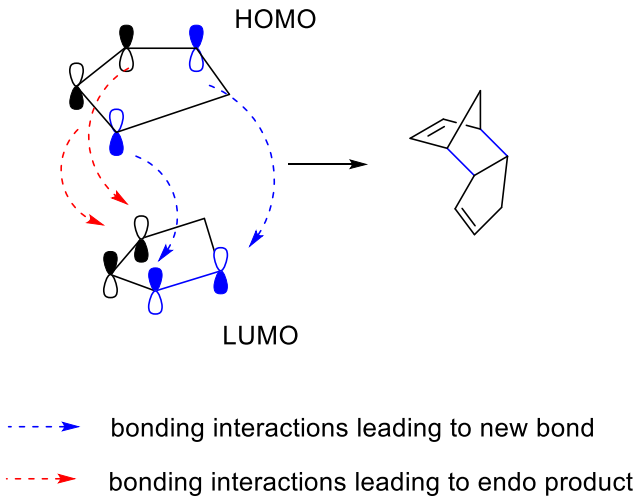
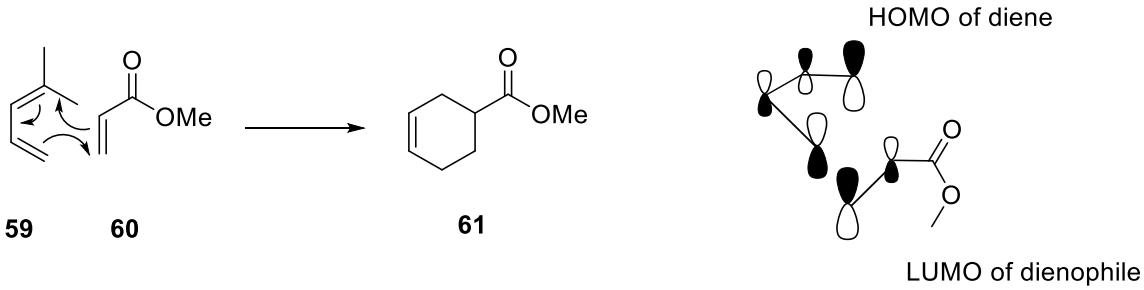


Figure 1.15 Orbital interactions leading to preferential endo product formation in the dimerization of cyclopentadiene

The regioselectivity of the Diels-Alder cycloaddition depends on the coefficients of the p-orbitals of dienes and dienophiles with the largest orbital coefficients bonding together. The coefficients are calculated through computational calculations, which shows a distortion in the LUMO of the dienophiles (larger orbital coefficient on the β-carbon) leading to a maximum overlap with the end of diene having larger orbital coefficients (Scheme 1.11).



59 60 61

Scheme 1.11 Regioselectivity in Diels-Alder cycloaddition

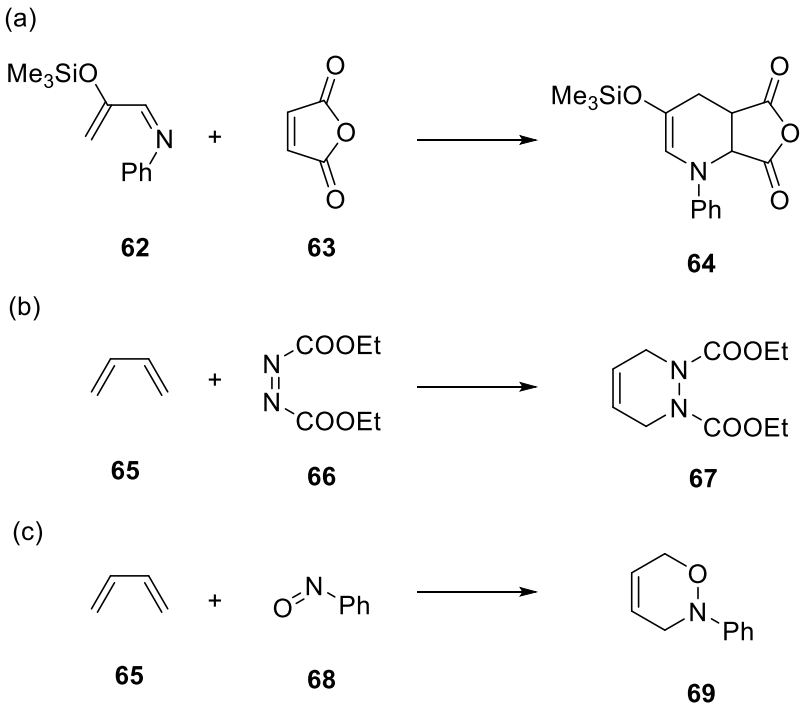
Hetero-Diels-Alder Cycloaddition

Hetero-Diels-Alder reaction involve either hetero-diene or hetero-substituted alkenes which undergo cycloaddition. A Diels-Alder reaction usually proceeds by the overlap of the LUMO of the dienophile and the HOMO of the diene. However, due to the electron-withdrawing nature of the hetero-substituted diene, the reduction in the activity of the hetero-diene is compensated by the introduction of electron-donating groups on the alkenes. This results in the 'inverse electronic demand', as now the HOMO of the alkene overlaps the LUMO of the hetero-diene.

For example tetrahydropyridine derivatives are readily formed by the Diels-Alder cycloaddition of 1-azadiene (**62**) with activated alkenes.[56] The two carbonyl groups in the maleic anhydride (**63**) activate the dienophile to give the product **64** (Scheme 1.12a).

The other two examples involve the use of a hetero-substituted dienophile like a diazo compound (**66**) or nitroso compound (**68**), which undergo cycloaddition with a diene (**65**) to provide pyridazine (**67**) or 1,2-oxazine (**69**) as the product respectively (Scheme 1.12b, 1.12c).[4] The hetero-Diels-Alder reaction has been applied extensively in natural product synthesis.[57,58]

Hetero-Diels-Alder and 1,3-dipolar cycloaddition are the most common studied cycloadditions for the synthesis of 5- and 6-membered heterocycles.[8]



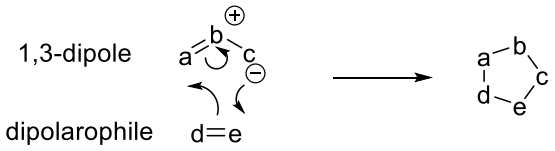
Scheme 1.12 Hetero-Diels-Alder cycloaddition of hetero/dienes with hetero-substituted alkenes

1,3- Dipolar cycloaddition

The origin of the concept of 1,3-dipolar cycloadditions can be traced back to a review article published on the chemistry of diazoalkanes by Rolf Huisgen in 1955.[59] The possible resonance structures of CH_2N_2 lead Huisgen to realise that it could be extended to a series of similar structures, in which elements of carbon, nitrogen and oxygen could be permuted. Such permutation lead to 18 different 1,3-dipoles of either the propargylic-allenylic or of allyl type based on the valence-bond theory.[60] A 1,3-dipole is a neutral species that has a principle canonical resonance form which can be represented by a separation of charge over three atoms. The structures of 1,3-dipoles reported till now are illustrated in Figure 1.16.

In this group of reactions, a 1,3-dipole undergoes a [3+2] cycloaddition with a saturated bond forming a 5-membered heterocyclic ring (Scheme 1.13). The pioneering work of Huisgen on 1,3-dipolar cycloadditions resulted in 94 full papers, 109 communications and 28 review articles (as of 1994) as mentioned in Huisgen's autobiography.[61] On present day, more than 1240 references related to 1,3-DC can be found by Scifinder search. It has had a highest impact on heterocyclic chemistry as it offers a powerful tool for the construction of 5-membered heterocycles, finding applications in various scientific disciplines including, synthetic organic

chemistry, dendrimer and polymer chemistry,[62,63] material sciences,[64] bio-conjugation,[65,66] and medicinal chemistry.[49,67]



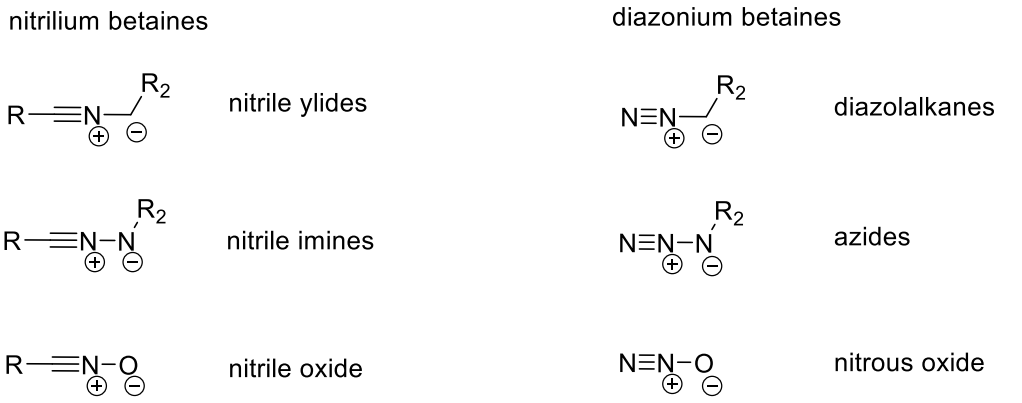
Scheme 1.13 Typical representation of a 1,3-dipolar cycloaddition reaction

Given their importance in organic chemistry,[49] numerous theoretical studies have been undertaken to rationalise the reactivity and selectivity of 1,3-dipolar cycloaddition reactions. Even though centuries has passed since their first description, there is still an ongoing debate on whether 1,3-diplar cycloaddition reactions have a concerted or a stepwise mechanism. Huisgen argued in favour of a concerted process (sometimes can be asynchronous) based on kinetic and stereochemical results, along with substituent and solvent effects.[68,69]

The lack of rate difference between alkene and alkyne dipolarophiles and the lack of solvent effect on the reaction, led Firestone to postulate a stepwise *syn*-diradical mechanism.[70] Firestone argued that first one σ-bond is formed preferentially and then the resultant diradical intermediate cyclises prior to bond rotation and thus retain the observed stereochemistry. In 2008, Houk *et al.* carried quantum chemical calculations to compare concerted *vs* stepwise transition states and concluded that concerted pathways are favoured over stepwise.[71] Although, some cases do exist where stepwise mechanisms precede over the concerted pathways.

Many theories for the mechanism of 1,3-dipolar cycloaddition have been proposed recently based on computational studies such as the Transition state distortion theory[71] and unified reaction valley approach (URVA).[72] The transition state distortion theory suggests that a significant distortion of the 1,3-dipole geometry would be needed to achieve the TS geometry of maximum overlap. Calculations of the distortion energies and the bond angle change of dipoles and dipolarophiles revealed that the majority of the transition state distortion energy (~80%) arised from deformation of the 1,3-dipole due to angle change, whereas the dipolarohile account for 20% of the total distortion energy. Whereas the URVA studies suggest that the mechanism is determined early in the van der Waals range where the mutual orientation of the reactants decides on charge transfer, charge polarization, the formation of radicaloid centers and the asynchronicity of bond formation.

1,3-dipoles of propargyl-allenyl type



1,3-dipoles of allyl type

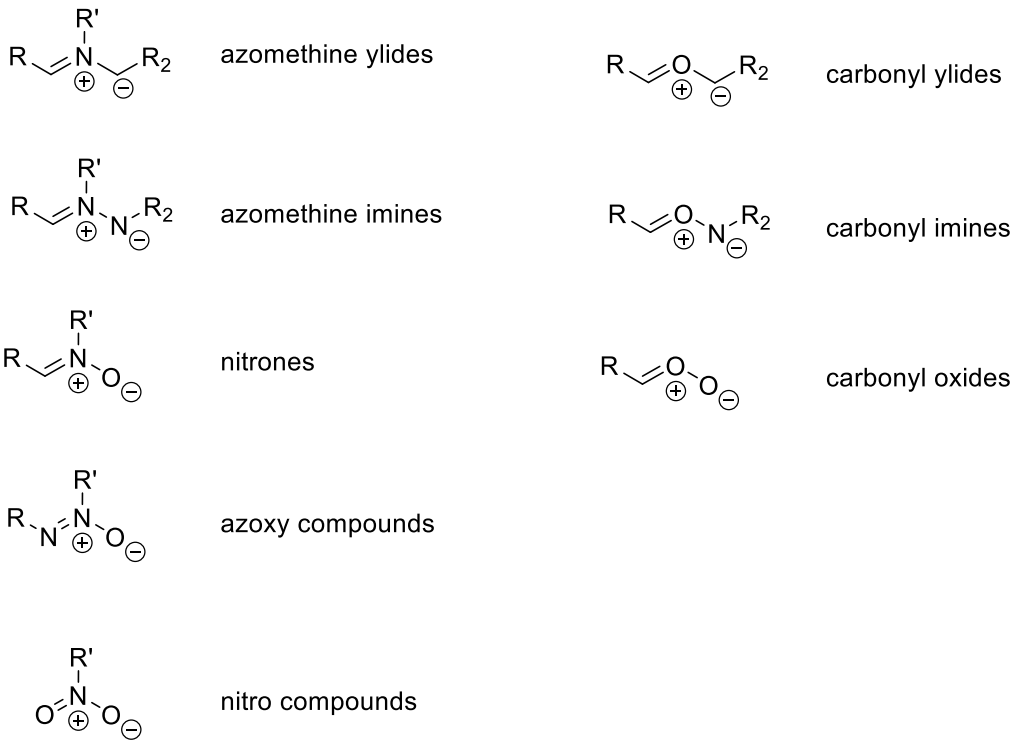
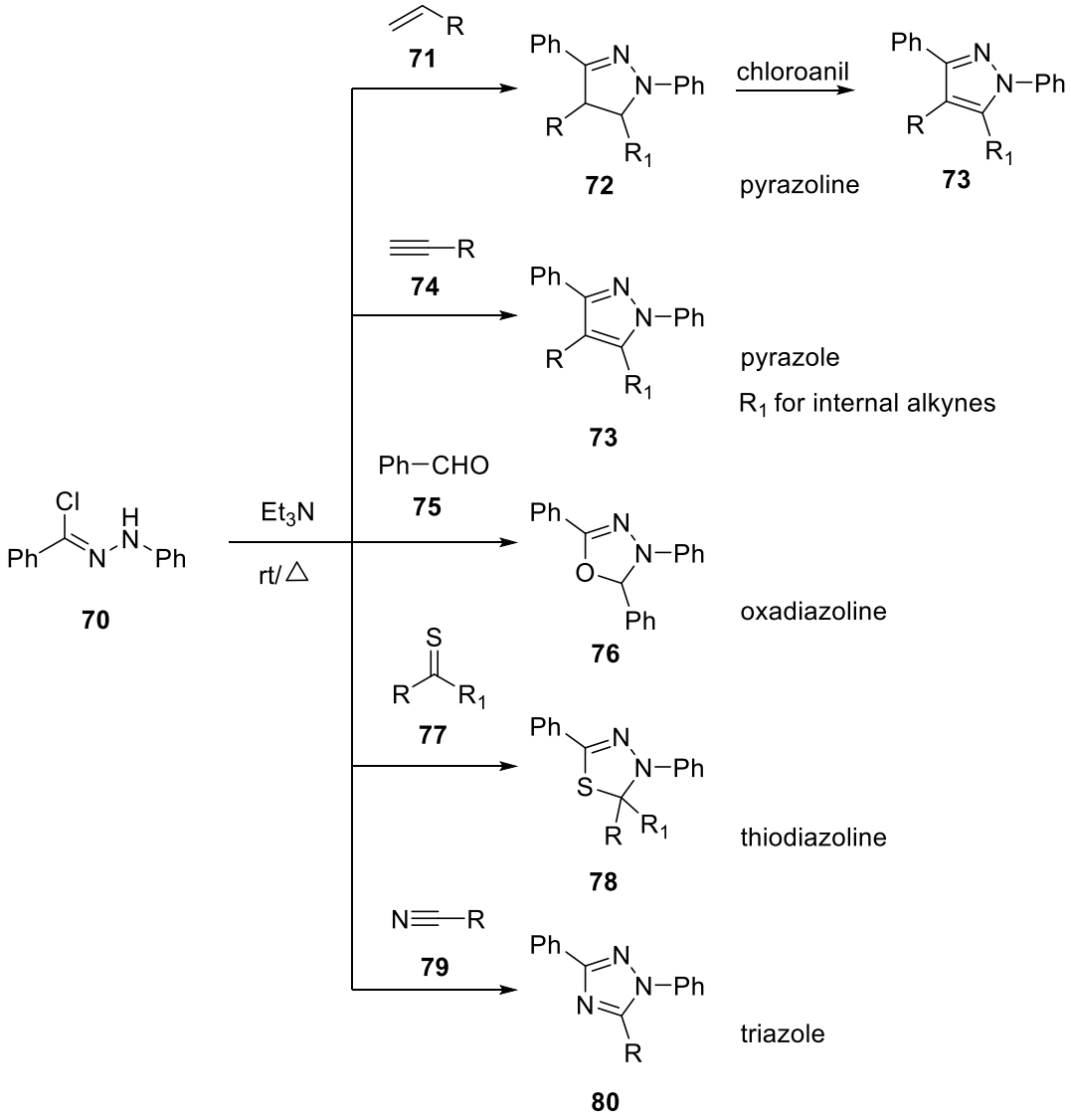


Figure 1.16 Structures of the 1,3-dipoles – propargyl-allenyl type and allyl type

Early examples of Husigen 1,3-dipolar cycloaddition

Some of the earliest examples of 1,3-dipolar cycloaddition involve nitrile imines, nitrile ylides and azomethine ylides as the 1,3-dipoles. Huisgen carried out the reactions of the 1,3-dipoles with suitable dipolarophiles like alkene, alkyne, imine, carbonyl (C=O), thiocarbonyl (C=S)

and nitriles to form the corresponding five membered heterocycles.[60,73] The cycloaddition of nitrile imine derived from **70** with various dipolarophiles is depicted in Scheme 1.14. With alkenes and alkynes, nitrile imine forms pyrazoline (**72**) and pyraozle (**73**). It forms oxadiazoline (**76**), thiadiazoline (**78**) and triazole (**80**) with benzaldeyde, thiocarbonyl compounds and nitriles respectively.



Scheme 1.14 1,3-dipolar cycloadditions of nitrile imine with various dipolarophiles

Similarly, nitrile oxides have been generated *in situ* and reacted with dipolarophiles like alkene, alkynes to give isoxazoline and isoxazole respectively. Cycloadditions with C=O and C=S and C=N and C≡N dipolarophiles gave dioxazole, 1,4,2 oxathiazole, 1,2,4-oxadiazoline and 1,2,4-oxadiazole respectively.[60] A direct application of the dipolar cycloaddition is well-represented in the synthesis of the anti-inflammatory drug Celecoxib (containing pyrazole), which was

obtained by a cycloaddition between a nitrile imine and an enamine.[74] The regioselective issues in its synthesis by carbonyl condensation route was overcome in this case.

FMO of [3+2] cycloaddition

While the debate was ongoing if the cycloadditions were concerted or followed a diradical mechanism, FMO (Frontier Molecular Orbital) theory provided a rationale for the observed reactivity and regioselectivity. In the FMO approach, the energies of the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) of the 1,3-dipoles and the dipolarophiles were calculated, together with the molecular orbital (MO) coefficients of the reacting centers.

HO orbital energies are derived from ionization potential data obtained by photoelectron spectroscopy, the value if which is negative of the orbital energy (Koopman's theorem). LU orbital energy is the negative of electron affinity of molecule, and are also calculated from the reduction potential, charge transfer energies or sometimes UV spectral data.[75]

Sustmann suggested that as the two addends start to approach each other, their orbitals (HOMO and LUMO) begin to interact and orbitals of suitable symmetry are formed.[76] The stabilisation of the MO is a direct function of the energy gap between the two frontier orbitals: lesser the energy gap, more the stabilisation. The energy gap of the interactions [HOMO(1,3-dipole)/LUMO(dipolarophile) and LUMO(1,3-dipole)/HOMO(dipolarophile)] are compared, and the FMO interaction corresponding to the lower value is presumed to play the dominant role (Figure 1.17).

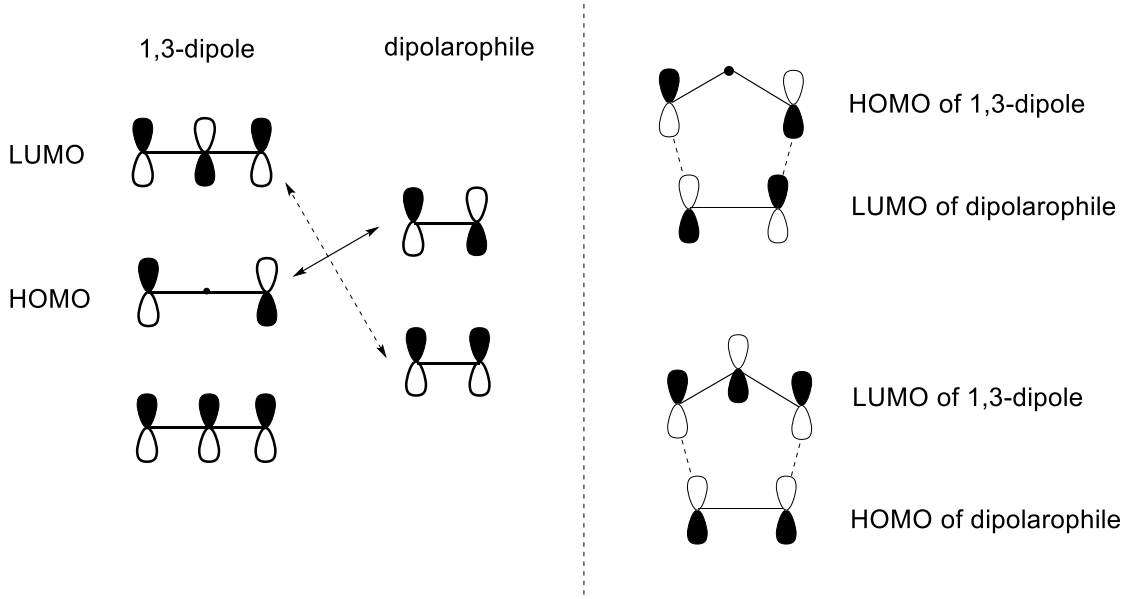


Figure 1.17 FMO interaction of 1,3-dipoles with dipolarophiles[76]

First order perturbation theory was used to predict the effect of the substituents on the orbital energies. Electron-withdrawing substituents lower the energy and electron-donating substituents increase the energy. An analysis of the energy diagrams of the FMO indicated that the reactivity increased as the dipole HOMO was raised and dipole LUMO was lowered.

Based on dominant FMO interaction and the direction of charge transfer, Sustmann classified 1,3-dipolar cycloaddition into three types[76] (Figure 1.18):

Type 1: HO controlled

In Type I, the smallest FMO gap exists between dipole HOMO and dipolarophile LUMO. Nucleophilic dipoles (like diazomethanes, nitrile imines, nitrones, azides and other ylides) with high lying HOMO orbitals and electrophilic dipolarophiles with low lying LUMO are involved in the cycloaddition leading to a cycloadduct. Thus electron-donating groups on dipole and electron-withdrawing groups on dipolarophile lead to an increase in reactivity by lowering the energy gap between the two frontier orbitals.

Type 2: HO-LU controlled

In Type II, the FMO gaps are equivalent between dipole HOMO-dipolarophile LUMO and vice versa. A dipole of this class is referred to as a HOMO-LUMO controlled dipole or an ambiphilic dipole, which includes nitrile imide, nitrone, carbonyl oxide, nitrile oxide, and azide. Increase in either frontier orbital energies will accelerate the reaction. For example, azides react with various electron-rich and electron-poor dipolarophile with similar reactivities.[77]

Type 3: LU controlled

In Type III, smallest FMO gap exists between dipole LUMO and dipolarophile HOMO. Electrophilic dipoles like ozone and dipolarophiles containing electron-donating groups bring the gap closer. Substituents which lower the dipole LU energy or raise the dipolarophile HO energy accelerate LU controlled reactions.

The above classification is based on the simplified FMO model which only takes the frontier orbital energies into account, but a complete perturbation expression involves other factors like repulsion factors (closed shell and coulomb constants) and charge transfer stabilisation.[78] However, the use of only frontier orbitals have been well supported by experimental results.

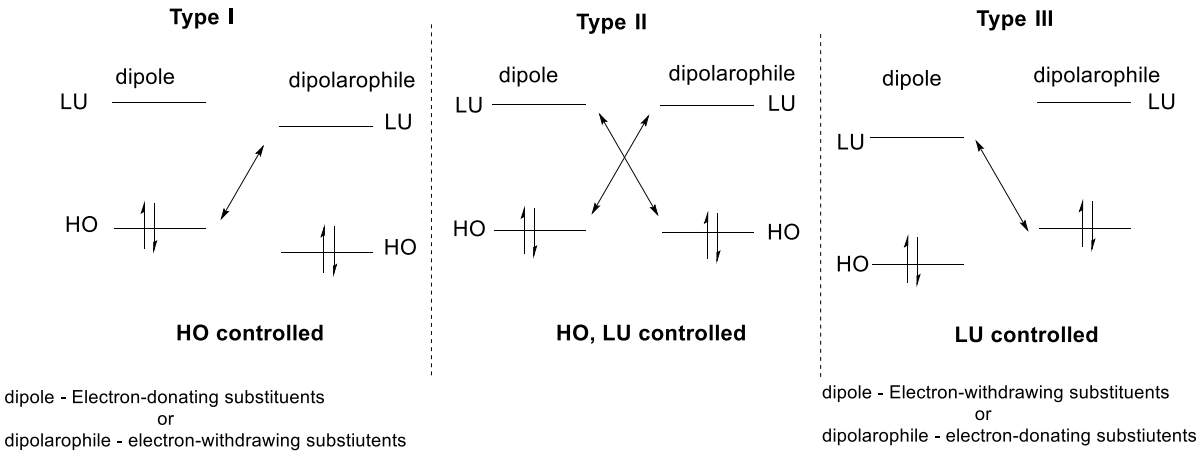


Figure 1.18 Classfication of 1,3-dipolar cycloaddition according to the FMO inetractions

The regioselectivity in cycloaddition is dependent on the terminal coefficients of the frontier orbitals.[75,78] The CNDO/2 calculated frontier orbital coefficients indicate that the HOMO of almost all 1,3-dipoles have larger values at the anionic terminus 'c' whereas, LUMO has the largest values at the neutral terminus 'a' (Figure 1.19). Exceptions include nitrile ylides and symmetrical dipoles. The preferred regio-isomer would be the one in which the atoms with the larger terminal coefficients (a-d and c-e) of the frontier orbitals interact. Case (a) would be more stabilised than case (b), resulting in stronger interaction and leading to cycloaddition products (Figure 1.19).

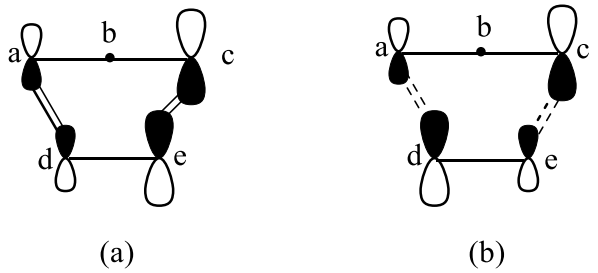
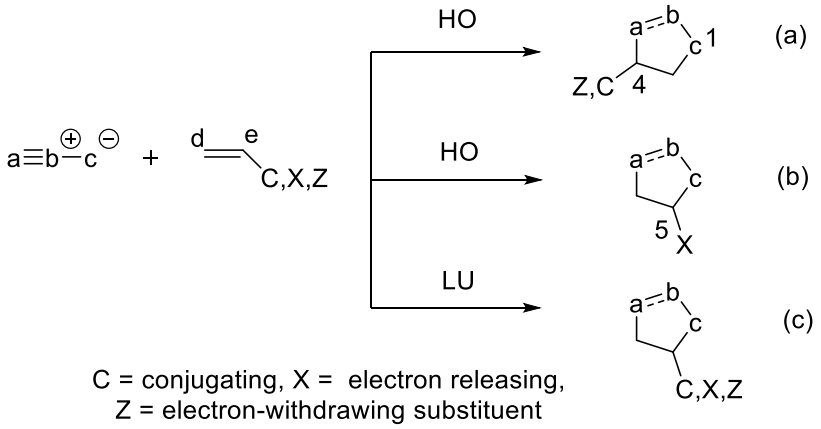


Figure 1.19 Schematic representation of greater stabilisation of transition state (a) than (b) due to different coefficient magnitudes

In the dipole-HOMO controlled cycloadditions, products with substituent remote from the anionic terminus 'c' are obtained (4-substituted) in case of electron deficient and conjugated dipolarophiles (larger coefficient at unsubstituted carbon 'd' in LUMO). Whereas in case of electron-rich dipolarophiles (larger coefficient at substituted carbon 'e'), 5-substituted products are obtained (Scheme 1.15a and 1.15 b; Figure 1.20)



Scheme 1.15 Regio-selective products formed in 1,3-dipolar cycloaddition[78]

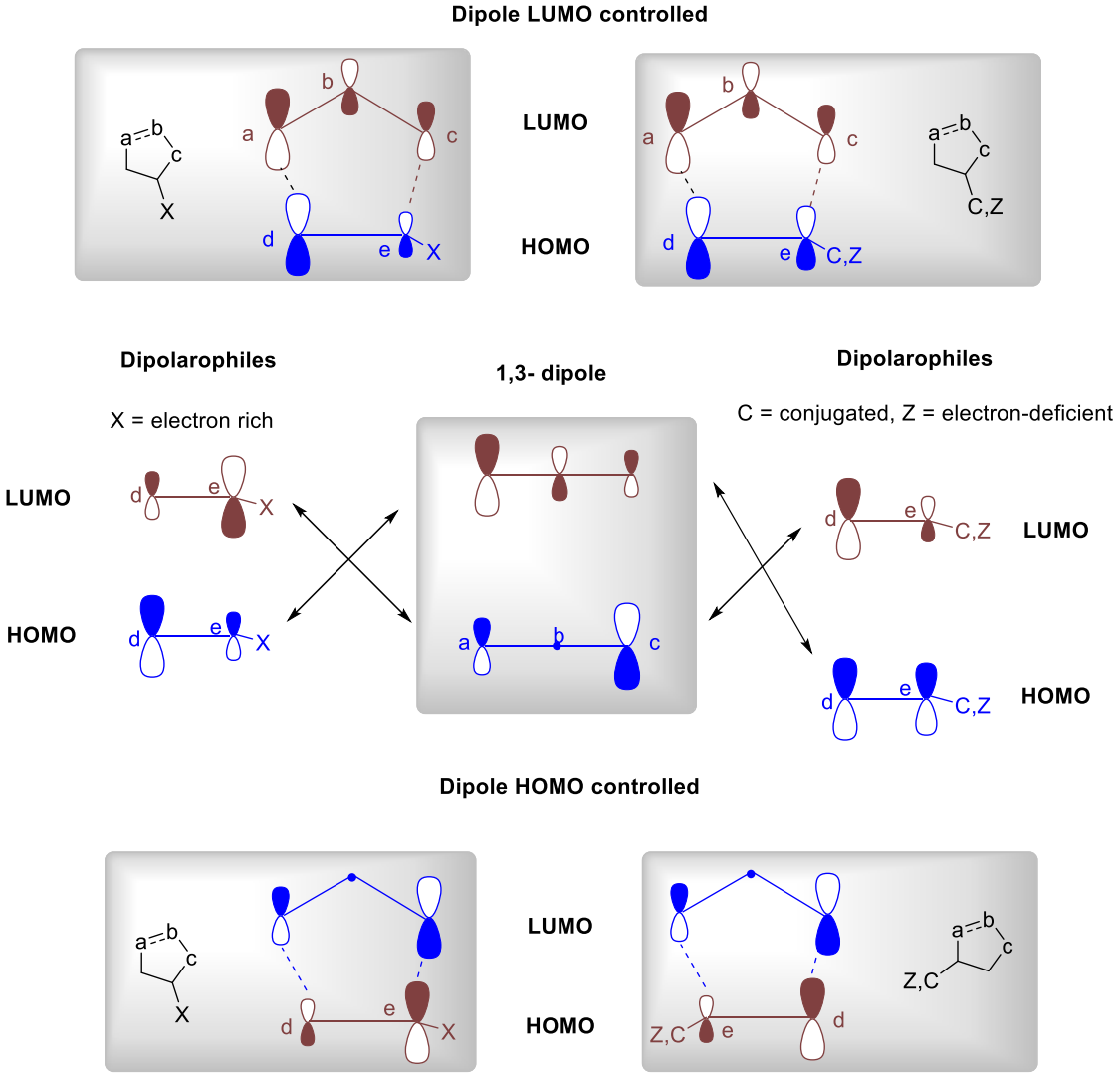


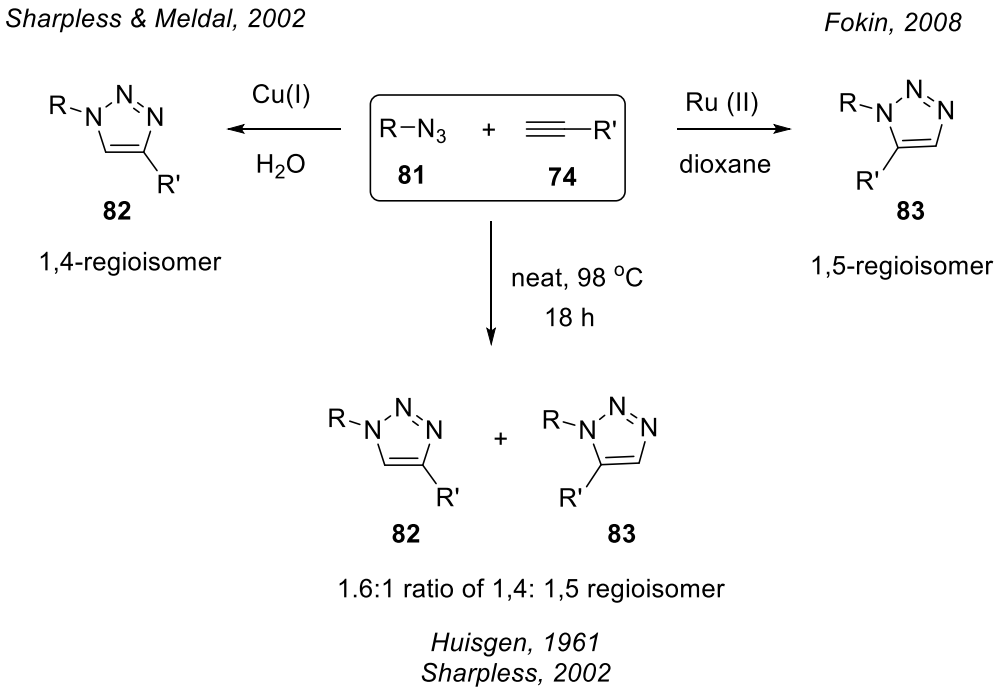
Figure 1.20 FMO interactions and the role of orbital coefficients in imparting regio-selectivity

Larger coefficients for the neutral terminus 'a' being present in the LUMO-dipole, 5-substituted products are obtained in dipole-LUMO controlled cycloaddition for all dipolarophiles (electron-rich, conjugated and electron-deficient which have larger coefficients at unsubstituted carbon 'd') (Figure 1.20).

Hence, all 1,3-dipoles react with electron-rich dipolarophiles to give 5-substituted products, whereas for conjugated and electron-deficient dipolarophiles, the regiochemistry depends on the dominant frontier orbital interaction (dipole-HO or dipole-LU controlled) (Scheme 1.15a, 1.15b and 1.15c)

Azide-alkyne Huisgen cycloaddition

A 1,3-dipolar cycloaddition between an azide and a terminal/internal alkyne to give a 1,2,3-triazole, called the Huisgen azide-alkyne cycloaddition was one of the earliest examples of the use of azide as a 1,3-dipole. The reaction, first realised by Huisgen,[79] gave a mixture of 1,4-substituted and 1,5-subsitituted triazoles after heating the starting materials neat at 98 °C for 18 h (Scheme 1.16). Since the difference in HOMO-LUMO energy levels for both azides and alkynes are of similar magnitude, both dipole-HOMO- and dipole-LUMO-controlled pathways operate in these cycloadditions leading to a mixture of regioisomeric 1,2,3-triazole products.



Scheme 1.16 Cu(I) and Ru(II) catalysed azide-alkyne click reactions

Copper-catalysed Azide-Alkyne Cycloaddition (CuAAC)

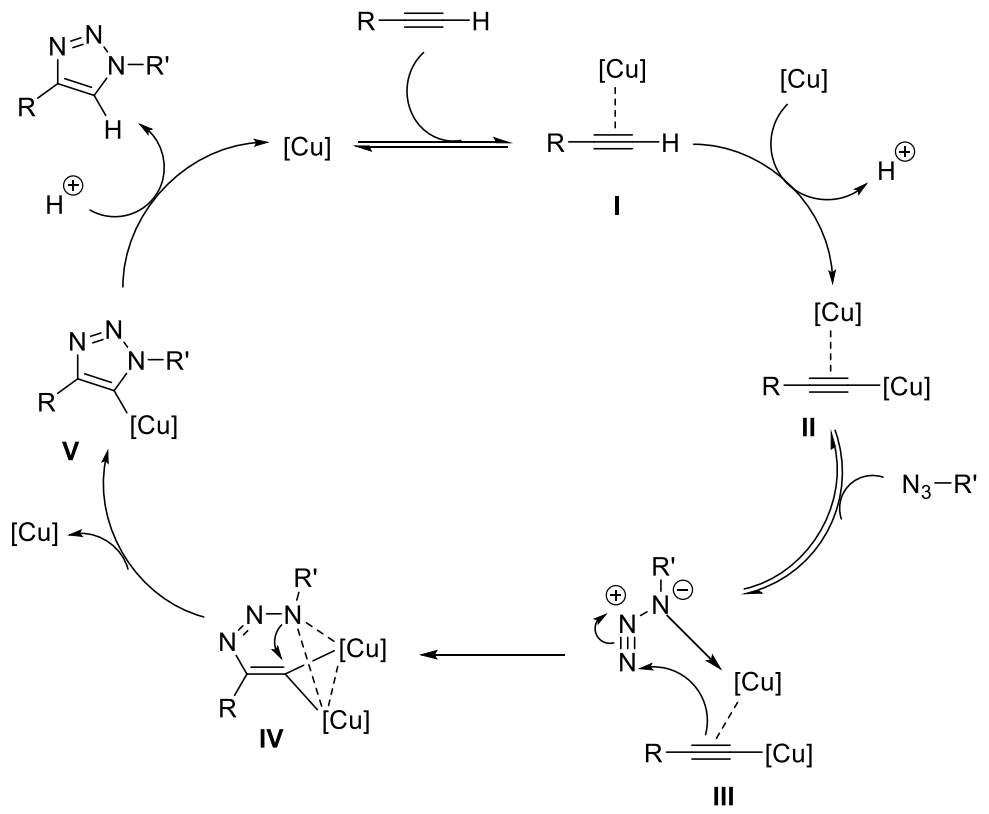
A notable variant of the Huisgen cycloaddition was the Cu(I) catalysed variant in which the organic azides and terminal alkynes are united to afford 1,4-regioisomers of 1,2,3-triazoles as sole products (Scheme 1.10). This reaction was first reported in 2002 independently by Morten Meldal[80] and K. Barry Sharpless group.[81] The reaction goes through a stepwise mechanism and is termed as Copper (I)-catalysed Azide-alkyne Cycloaddition (CuAAC). Although Cu(I) such as cuprous iodide and cuprous bromide have been used, the most common method involves the *in situ* generation of Cu(I) by using a mixture of copper (II) sulfate and a reducing agent like sodium ascorbate in water.[82] It is considered one of the best click reactions,[83] with an enormous rate acceleration of 10^7 to 10^8 compared to un-catalysed 1,3-dipolar cycloaddition. It succeeds over a broad temperature range, insensitive to aqueous conditions and a pH range over 4 to 12, and tolerates a broad range of functional groups. Pure products are often isolated by simple filtration without the need for column chromatography.

After the introduction of CuAAC in 2002, numerous advances in this reaction have taken place and have found application in bioconjugation[66] (labelling), material science[84] (polymers, dendrimers) and drug discovery.[67,85,86]

The mechanism for the CuAAC had been elusive until recently owing to the challenges involved in the direct study of copper catalysis. The first mechanism proposed by Sharpless et al. involved a mononuclear copper complex as the reactive intermediate.[81] Over a period of time, different experimental as well as theoretical studies pointed towards possible involvement of poly nuclear copper (I) intermediates in the reaction.[87–89] In 2013, Fokin et al. reported a direct evidence of a dinuclear copper intermediate (**III**) through calorimetry and crossover experiments[90] (Scheme 1.17).

Through the heat-flow calorimetry experiments performed on a representative cycloaddition process, they found that monomeric copper acetylide complexes were not reactive towards azide unless an exogenous copper catalyst was added. Further involvement of the role of two copper atoms was proved through cross-over experiments with an isotopically enriched exogenous copper source.

A catalytic cycle of CuAAC was proposed[90] - activation of σ-bound copper acetylides (**I**) (both terminal and formally internal) by a weak and reversible π-interaction with a copper centre. The σ-bound copper acetylide **II** bearing a π-bound copper reversibly co-ordinates the azide, forming the complex **III** (Scheme 1.17)



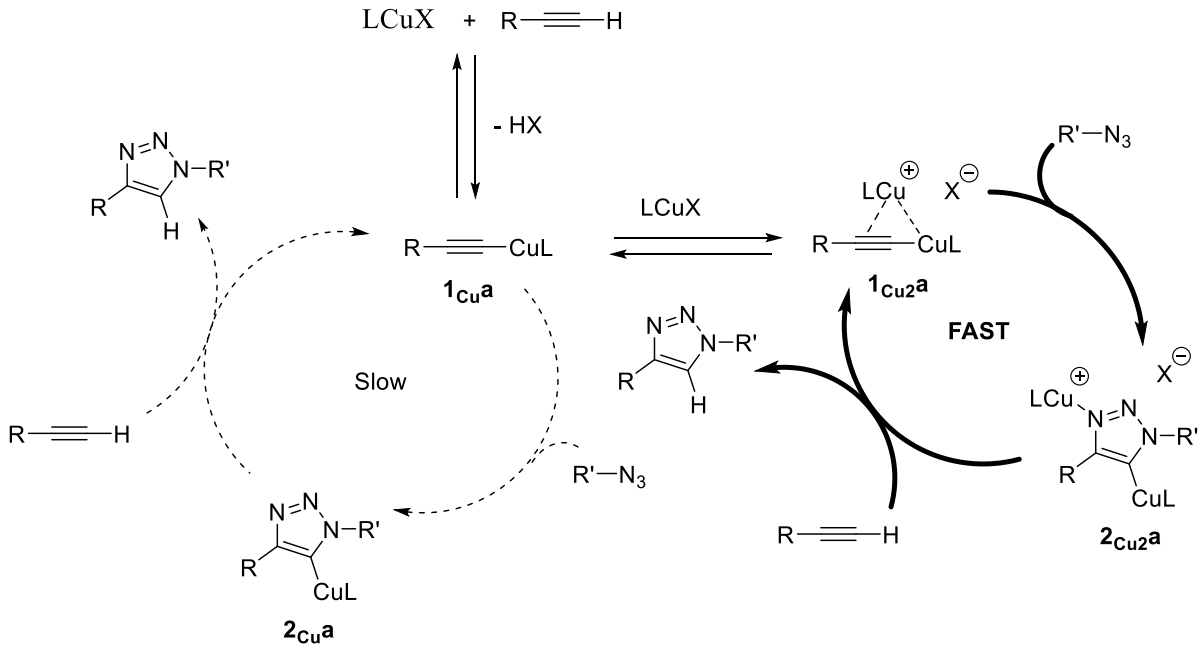
Scheme 1.17 Fokin's proposed catalytic model for CuAAC with two copper atoms[90]

Nucleophilic attack at *N*-3 of the azide by the β-carbon of the acetylide forms the first covalent C-N bond which leads to an unusual 6-membered copper metallacycle **IV**. Ring contraction to a triazolyl-copper derivative **V** is followed by protonolysis which delivers the triazole product and closes the catalytic cycle (Scheme 1.17).

The dinuclear complex of π, σ -bis copper acetylide **II** was qualified as a non-isolable and highly interactive intermediate by Fokin and group. Although in 2015, Bertrand and colleagues[91] were successful in isolating the intermediate (**1_{Cu2}a**; Scheme1.18) by stabilizing it with cyclic (alkyl)(amino) carbenes (CAACs) ligand. They also isolated the mononuclear copper (I) intermediate (**1_{Cu}a**; Scheme 1.18) and an unprecedented bis-metallated triazole complex (**2_{Cu2}a**) as key intermediate in CuAAC (Scheme 1.18).

The isolation of the mononuclear complex and experimental kinetic studies indicate that both mono and di nuclear complexes promote the cycloaddition, although the di nuclear complex **1_{Cu2}a** is the kinetically favoured pathway. The treatment of azide with all the three complexes, found an acceleration in the rate of reaction with both di-nuclear complexes as compared to the mono-nuclear complex. Although the reactions promoted by **1_{Cu2}a** and **2_{Cu2}a** proceed at the same rate, a short initiation period is observed with **1_{Cu2}a**, which is concomitant with the

formation of $\mathbf{2_{Cu2}a}$; after the initiation period, the concentration of $\mathbf{2_{Cu2}a}$ remains constant over the course of the catalytic reaction, indicating that $\mathbf{2_{Cu2}a}$ is the resting state of the catalytic cycle (Scheme 1.18).



Scheme 1.18 Bertrand's mono and bis-copper pathways for CuAAC[91]

The use of the ligand as well as the use of trifluoromethane sulfonate anion as the counter ion was responsible in forming a stable and isolable complex of both $\mathbf{1_{Cu2}a}$ and $\mathbf{2_{Cu2}a}$. The alkyne serves as the proton source for the demetallation of $\mathbf{2_{Cu2}}$, which regenerates the π,σ-bis(copper) acetylide of type $\mathbf{1_{Cu2}}$, leaving out complexes of type $\mathbf{1_{Cu}}$ from the catalytic cycle. Thus, the regioselective formation of 1,4-disubstituted triazole was attributed to the mechanism involving the role of 2 copper atoms working in tandem.

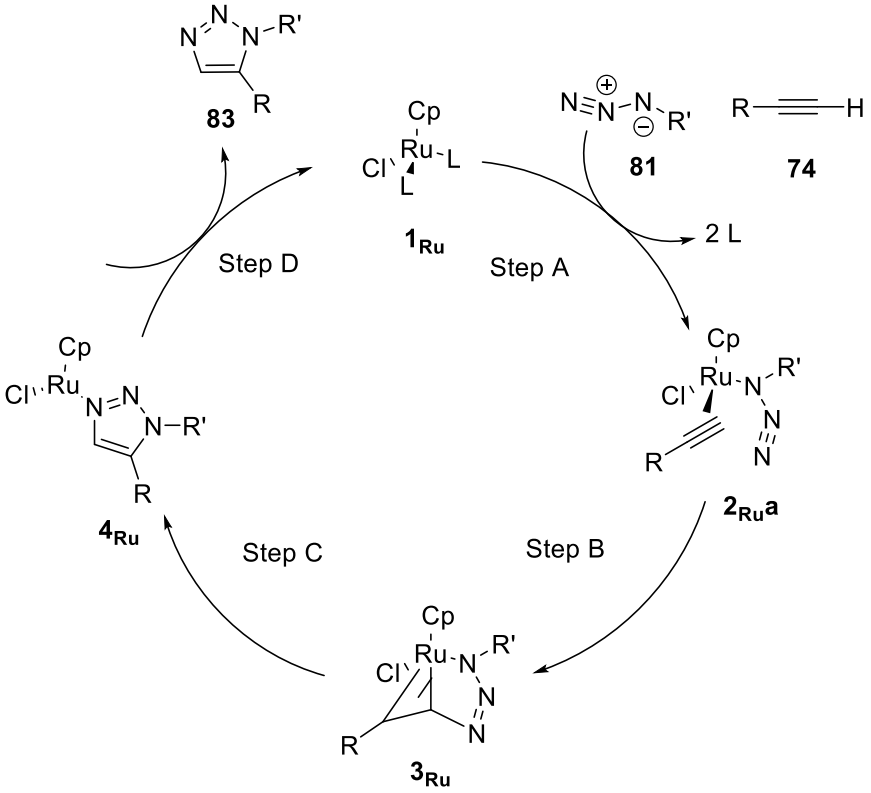
Ruthenium-catalysed Azide-alkyne Cycloaddition (RuAAC)

The 1,5-regioisomer of 1,2,3-triazole was obtained as the sole product when ruthenium (II) was used as a catalyst, giving rise to the term ruthenium-catalysed azide-alkyne cycloaddition (RuAAC)[92] (Scheme 1.10). As a result of the pioneering work of Fokin and colleagues, it was found that [Cp*RuCl] complexes, such as $Cp^*RuCl(PPh_3)_2$, Cp*RuCl(COD) and Cp*RuCl(NBD), were among the most effective catalysts. The catalytic activity of the ruthenium complexes, was attributed to the pentamethyl cyclopentadienyl ligands owing to their ability to stabilise the higher formal oxidation states of the metal centre. The complexes also promote the cycloaddition reactions of organic azides with internal alkynes, providing access to fully-substituted 1,2,3-triazoles, which was not observed with copper catalysts.

Unlike CuAAC, where copper acetylides were involved, the neutral [Cp*RuCl] was found to be the catalytically active species in RuAAC with no detection of ruthenium acetylides in the reaction. The chloride ion is found to have a prominent role as ruthenium catalysts with Br and I species were less active and the $[Cp^*Ru]^+$ cationic complexes were completely inactive.

The mechanism[92] of the RuAAC is depicted in Scheme 1.19. The displacement of the spectator ligands in $\mathbf{1_{Ru}}$ (step A) by azide and alkyne produces the activated complex $\mathbf{2_{Ru}a}$, which is converted, via the oxidative coupling of an alkyne and an azide (step B), to the ruthenacycle $\mathbf{3_{Ru}}$. This step controls the regioselectivity, in which the new carbon-nitrogen bond is formed between the more electronegative (and less sterically demanding) carbon of the alkyne and the terminal electrophilic nitrogen of the azide.

Alkynes with a H-bond donor group (propargylic alcohols and amines) provided exclusive regioselectivity owing to the strong H-bond between alcohol/amine and the Cl^- ligand on ruthenium. The new bond always formed between the β carbon of the alkyne and the terminal N_2 of the azide.



Scheme 1.19 Proposed catalytic cycle for RuAAC[92]

DFT studies were carried out to ascertain the energy of different possible activated complexes of ruthenium with azide and alkyne (Figure 1.21). Out of the four different possible complexes

$\mathbf{2_{Ru}a}$, $\mathbf{2_{Ru}b}$, $\mathbf{2_{Ru}c}$, $\mathbf{2_{Ru}d}$, DFT calculations favoured $\mathbf{2_{Ru}a}$, with the azide co-ordinated to the metal through the proximal nitrogen (*N*-1) and the alkyne through the β-carbon. The nucleophilic attack of the alkyne on the terminal nitrogen of the azide (oxidative coupling) leads to the ruthenacycle $\mathbf{3_{Ru}}$.

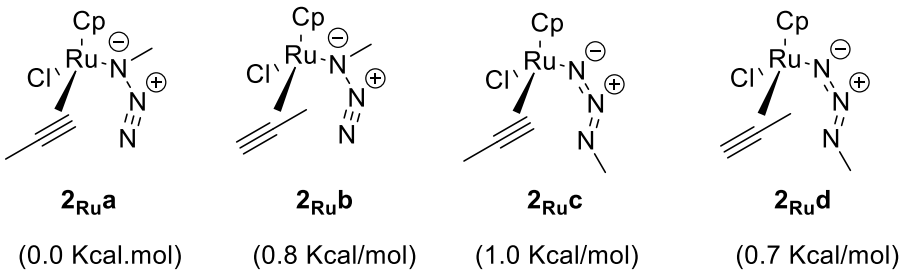


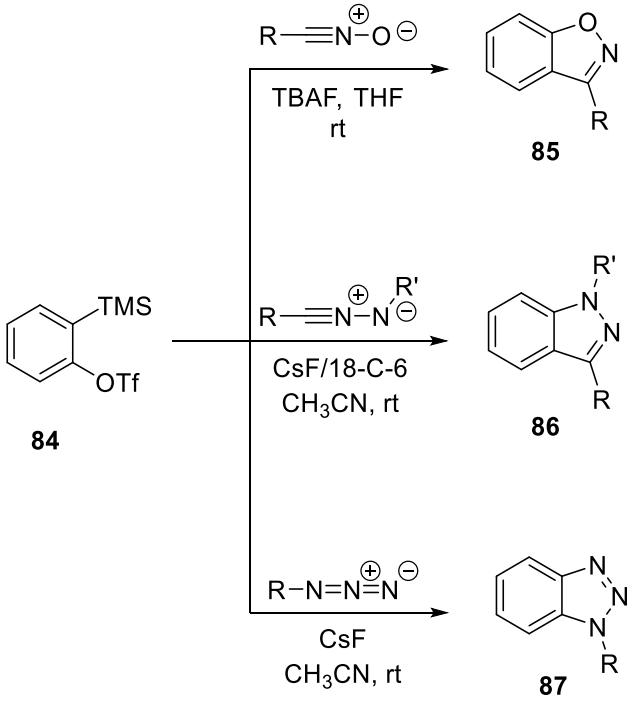
Figure 1.21 Structures and computed energies of activated complexes[92]

The metallacycle intermediate $\mathbf{3_{Ru}}$ then undergoes a rate-determining reductive elimination (step C) releasing the aromatic triazole product and regenerating the catalyst (step D) or the activated complex $\mathbf{2_{Ru}a}$. Extensive studies by Fokin *et al.*[92] indicate that the regioselectivity in RuAAC is determined by the oxidative coupling step, involving nucleophilic attack of the activated alkyne at the electrophilic terminal nitrogen of the azide.

***In situ* 1,3-dipolar cycloadditions**

Dipolar cycloadditions of the 1,3-dipoles with *in situ* generated dipolarophile have been of recent interest. In the development of novel synthetic methods for high through put synthesis, protocols which are reliable, efficient, precludes the use of too many reagents and generate inoffensive byproducts are quintessential.[67] In this regard an efficient coupling technology of *in situ* generated short lived reactive species utilizing single reagent are the best bargain. In this respect, a series of aryne click reactions have been developed with dipoles like nitrile oxides, nitrile imines and azides to give benzisoxazoles (**85**), 1*H*-indazoles (**86**) and benzisoxazoles (**87**) respectively (Scheme 1.20).[93] Both arynes and the 1,3-dipoles are generated in a single-pot using fluoride ion sources like CsF and TBAF, which on cycloaddition yield the cycloadducts **85-87**.

Thus, cycloadditions particularly 1,3-dipolar cycloadditions provide a great synthetic route towards various 5-membered heterocycles.



Scheme 1.20 1,3-dipolar cycloaddition of *in situ* generated arynes and various 1,3-dipoles

1.7 Cyanamides- Chemical History

Cyanamide was first obtained by passing gaseous ammonia over cyanogen chloride in 1838.[94] Cyanamides are weak acids and basically feature a nitrogen atom bearing a nitrile group. The presence of the amino and the nitrile group provides cyanamides its unique duality as a 'nucleophile' and 'electrophile'. Also, cyanamide is known to exist in its two tautomeric forms- cyanamide and carbodiimide, cyanamide form being the more predominant (Figure 1.22).[95]

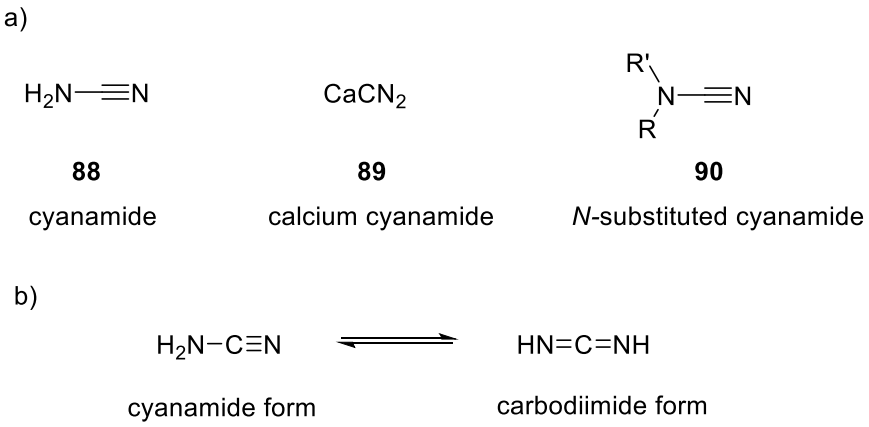


Figure 1.22 a) Cyanamide and its derivatives, b) tautomeric forms of cyanamide

1.7.1 Calcium Cyanamide

Two chemists Frank and Caro, in their quest for sodium cyanide (used for extraction of gold), started studying the absorption of nitrogen by carbides. They heated barium and calcium carbide and found that both the carbides absorbed nitrogen on heating giving barium cyanide and calcium cyanamide (identified later in 1898 by Rothe, equation 1, Scheme 1.21). They filed a patent for this process in 1895 which came to be known as the Frank Caro process.[96]

$$CaC_2 + N_2 \xrightarrow{1000 - 1600\ ^oC} CaCN_2 + C \qquad (1)$$

$$CaCN_2 + 3H_2O \longrightarrow CaCO_3 + 2NH_3 \qquad (2)$$

ammonia release

Scheme 1.21 Synthesis of calcium cyanamide and its reaction with water

The accidental discovery of calcium cyanamide lead to its use as a fertiliser, when Caro observed that calcium cyanamide in presence of water releases ammonia in the soil (equation 2, Scheme 1.21). Industrial production of calcium cyanamide was started in 1907, with a new refined process which lowered the operating temperature to 700-800 ^oC. The production reached 4000 tons/ year in 1908, and was a great success, such that Frank Washburn acquired the exclusive American and Canadian rights for the process. It became the beginning of one of the biggest chemical industry- American Cyanamid. Calcium cyanamide was further utilised for the production of ammonia, which was oxidised to nitric acid (nitrates used as explosives), the demand for which increased during the World War I.

Cyanamide and Nitrate Chemistry at War

The importance of 'Nitrogen Fixation' in soil was realised late (1886), when the only options for fixed nitrogen were bird and animal wastes which contained nitrates. One of the largest sources of this fixed nitrogen was found in Chile. Over thousands of years, the deposits of bird droppings, a vast number of which nested on the coast of Chile resulted in the "natural" deposits called "Guano". A huge industry developed to supply this Chilean saltpetre (sodium nitrate) to the rest of the world, which came to be entirely dependent on the Chilean resource for fertilisers and high explosives.

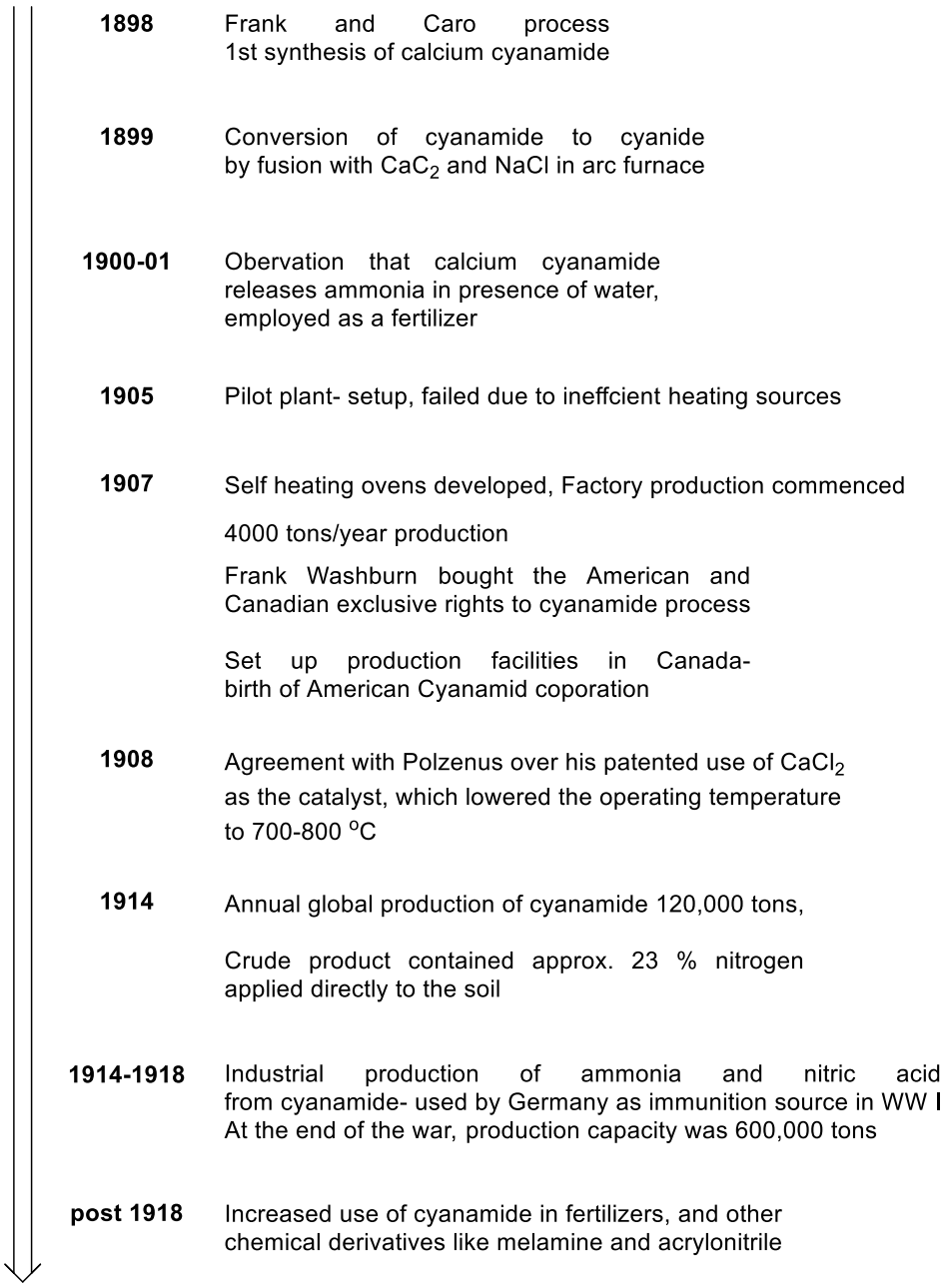


Figure 1.23 Historical timeline of calcium cyanamide

Concerns over the depletion of Chilean reserves and its monopoly stimulated European scientists to explore the direct fixation of atmospheric nitrogen. The challenges of nitrogen fixation, and its implications were intricately expressed by Ostwald in 1903, '*The significance for bound nitrogen…is especially high for both war and peace…Without saltpetre the best military is almost helpless…Were war to break out today between two great powers, one of which was able to prevent the export of saltpetre from Chile's few harbours, that ability alone would render its opponent almost incapable of fighting*". [97] The solution of this nitrate problem seemed to be a strategic necessity, apart from its use in fertiliser.

Nitrates were essential to production of modern explosives mainly trinitrotoluene (TNT) and picric acid. In 1903, Berkeland and Eyde devised an electric arc which stimulated lightening, enabling the capture of atmospheric nitrogen in the form of nitric acid. It was reacted with limestone to form calcium nitrate which was used as a fertiliser (Figure 1.24). In 1904, Haber started working on the high pressure synthesis of ammonia from its elements. Bosch was responsible for the scaling up, and he set it up on an industrial scale, and the process came to be known as 'Haber-Bosch ammonia process.'[98] Production of ammonia started in 1913, which was converted to ammonium sulphate to be used as a fertiliser.

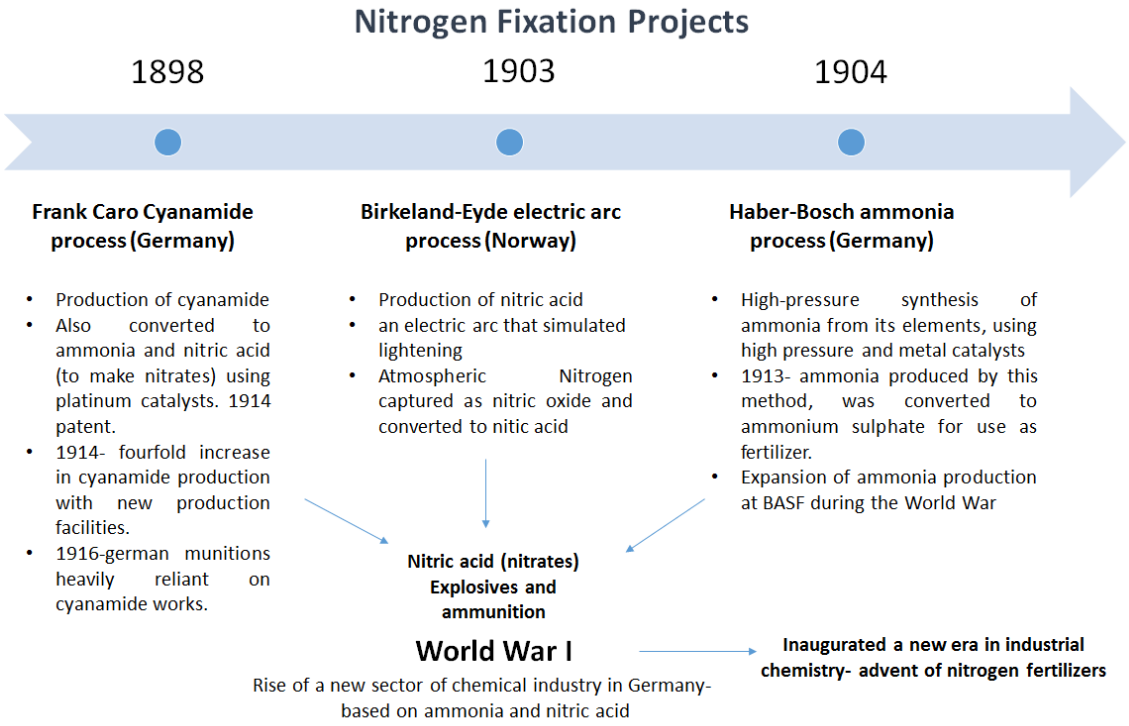


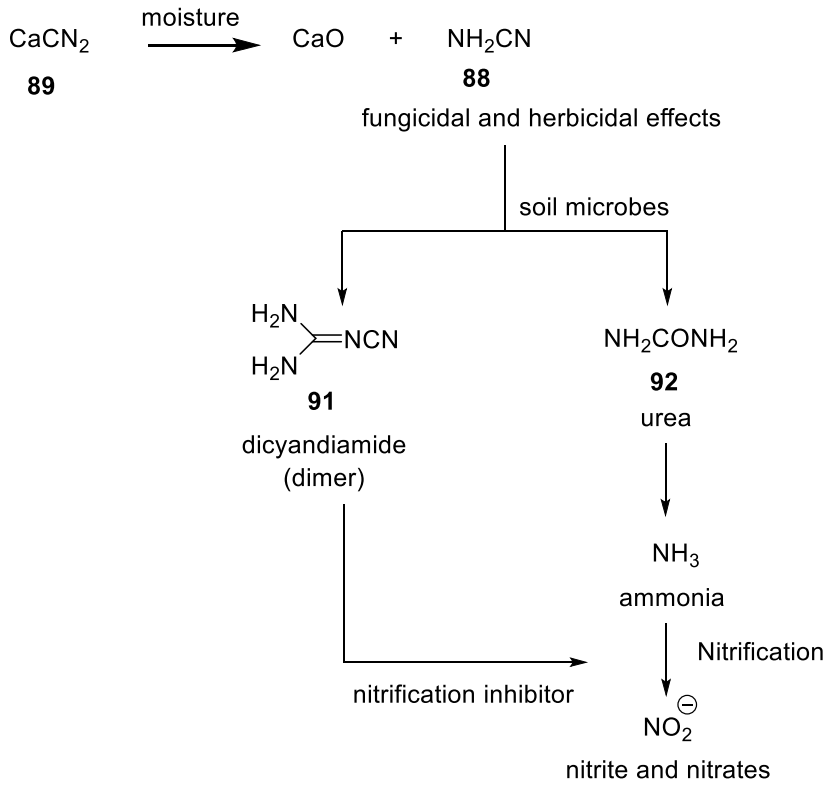
Figure 1.24 Cyanamide and World War I

The important conversion of ammonia to nitric acid gained importance for the use in explosives. In 1914, Frank and Caro developed a process for oxidation of ammonia using platinum catalysts. Synthetic ammonia, and oxidation of ammonia to nitric acid would not have gained much importance, unless for the beginning of the Great War (World War I). The restriction of the Chilean saltpetre by the British forces, forced the German government to upscale the production of nitrogen products, wherein all the cyanamide, Norwegian nitrogen as well as Haber-Basch ammonia process were expanded and production was carried out on a large scale. At the end of the war, Germany was producing more than 500,000 tons of nitrogen products annually, more than one-third of it coming from the cyanamide process, which was

to become the basis of the fertiliser industry. Thus, the World War and the role of nitrates, accelerated the productions of cyanamide and other nitrogen compounds.[99]

Calcium Cyanamide: Role in Agriculture and Chemical Industry

The importance of calcium cyanamide is that it was the first fully synthetic fertiliser ever achieved. Calcium cyanamide is used in agriculture mainly as a slow-release nitrogen fertiliser, which also exhibits beneficial side-effects against soilborne plant diseases, slugs and germinating weeds. The fertiliser is broken down by soil moisture into lime and free cyanamide which provides its herbicidal and fungicidal effects. The cyanamide is further converted to ammonia through urea by the soil microbes. A second pathway leads to dicyandiamide which acts as the nitrification inhibitor of the soil, wherein the conversion of ammonia into nitrate is slowed down for several weeks, thus preventing the leaching of nitrogen into the soil (Scheme 1.22).[100]



Scheme 1.22 The mechanism of action of calcium cyanamide as a fertiliser

Calcium cyanamide is also used to control animal pests on pasture, protection against gastric and intestinal parasites in grass, and salmonella in sewage. In present times, despite the availability of different fertilisers, calcium cyanamide is still widely used. This can be attributed to some peculiar properties, one being its high alkalinity, which is useful in acidic

soils or as a neutraliser with acidic fertilisers. Its ability to speed the equilibration in mixed fertilisers (from years to days) also makes it an important constituent for fertilisers. It is also effective as a scrubbing agent for removal of nitric oxide gases from waste gases.[100]

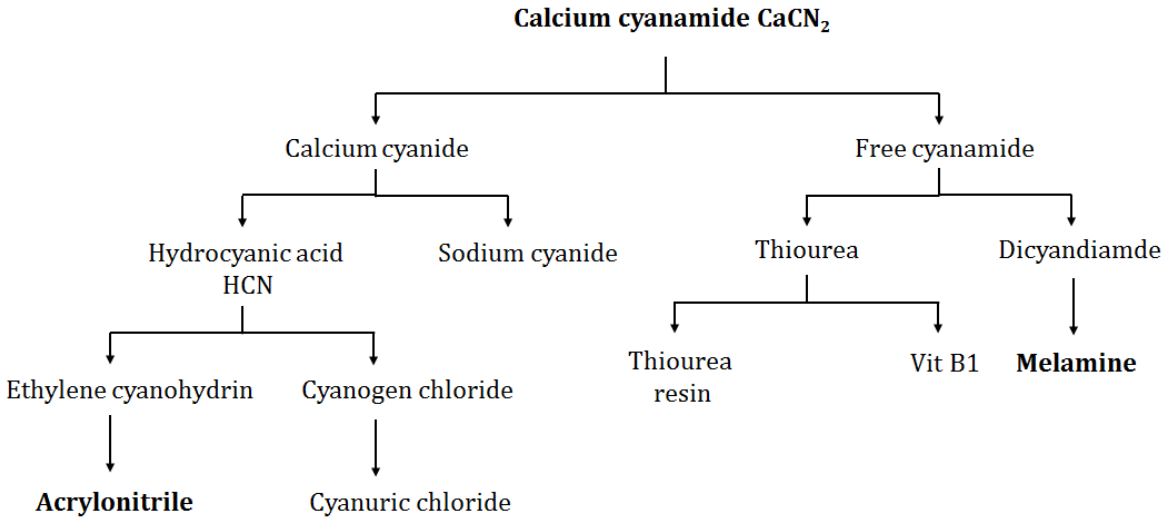


Figure 1.25 Derivatives of calcium cyanamide

Apart from its use as a fertiliser and herbicide, calcium cyanamide has been used for production of different chemicals, largest being the dimer preparation- dicyandiamide, which is further polymerised to get the trimer melamine (Figure 1.25). Melamine has been used in plastic resins for its strength, hardness, moisture and temperature stability. Most of these resins are used in molding compounds, but are also used to provide strength to paper, shrinkage control and crease resistance to wool and rayon, and in water-resistant laminates.[100]

Other commercial derivatives include cyanide derivatives, mainly calcium and sodium cyanide, which finds its use in extraction of gold in mines. Acidification of calcium cyanide yields hydrocyanic acid which is an important starting material for different chemical derivatives. One of the important being acrylonitrile, which is made by condensation of ethylene oxide to produce ethylene cyanohydrin, which is dehydrated to acrylonitrile (Figure 1.25).[100] It finds a wide use in the manufacture of synthetic rubber by copolymeriation with butadiene. Many other new uses are being explored, one being in the production of wool-like synthetic fibres.

Biological significance of Cyanamide

Cyanamide is produced naturally, by the plant- Hairy vetch (Vicia villosa) which produces it from inorganic nitrates.[101] It is an aldehyde dehydrogenase inhibitor, and blocks ethanol metabolism at acetaldehyde stage,[102] leading to toxic acetaldehyde syndrome on alcohol consumption, causing unpleasant symptoms in the alcohol-addict.[103]

It is also an important reagent in prebiotic chemistry, detected in interstellar clouds. Stanley Miller, in 1953 showed how amino acids could have formed on earth by sparking a gas mixture of methane, ammonia, water and hydrogen.[104] However, the formation of peptides from these amino acids proved a mystery. He conducted some experiments in 1958 to study the polymerisation of amino acids under simulated early earth conditions, however the analysis was never reported. The boxes of unanalysed experimental prebiotic samples were passed on to Jeffrey Bada, his second graduate student recently. These samples contained a potential prebiotic condensation agent- cyanamide. A recent analysis of these samples[105] prove that the addition of cyanamide while sparking the same mixture resulted in amino acids, dipeptides and diketopiperazines, thus indicating the importance of condensation agents like cyanamide in the origin of life. The studies indicated the formation of dicyandiamide formed by cyanamide dimerisation (in the simulated conditions) and its role as a prebiotic condensing agent, which could polymerise amino acids and lead to complex molecules like peptides. It has also been suggested to be involved in the synthesis of activated pyrimidine ribonucleotides and deoxynucleotides.[106]

Cyanamide finds use mainly in the agrochemical and pharmaceutical industry. It is also one of the key raw material for many herbicides, fungicides and insecticides like Amitriol, Bensulfuron, Pyrimethanil, etc. and anti-ulcer drug Cimetidine.[100] Moreover, many antiviral and anticancer drugs with pyrimidine and purine moiety are based on cyanamide and guanidine chemistry.

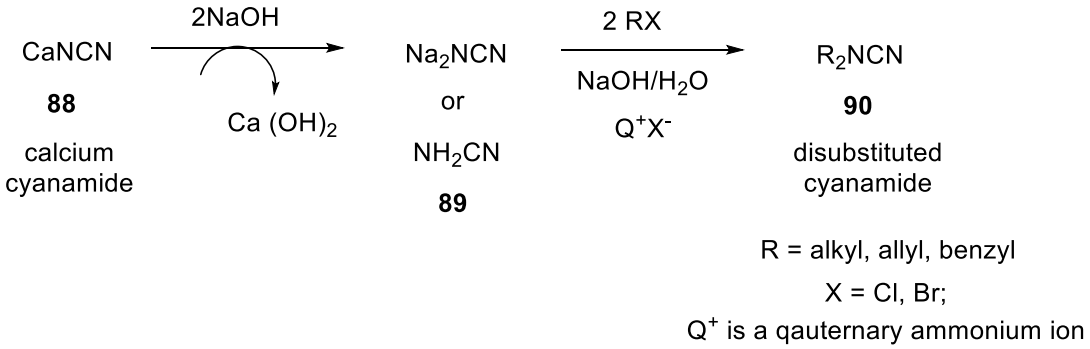
1.7.2 *N*-Substituted cyanamides

N,*N*-Disubstituted cyanamides and *N*-monosubstituted cyanamides with the NCN functionality provide a means for the various organic transformations at both the amino and the nitrile centre. Various advances have been made in the synthetic routes towards the synthesis of *N*-substituted cyanamides as well as their utilisation in heterocycle synthesis in the last two decades.[107,108]

1.7.2.1 Synthesis of N-Substituted Cyanamides

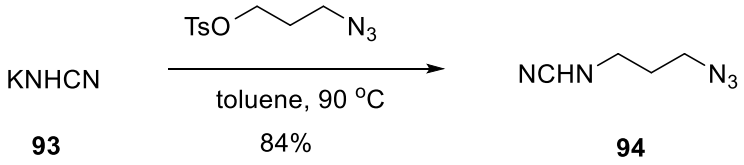
Early Synthesis

One of the earliest examples for the synthesis of dialkylcyanamides was based on the alkylation of sodium or calcium cyanamide in aqueous ethanol (1924).[109] The easy accessibility of calcium cyanamide salt then, made this an obvious choice of synthesis, however it was laborious and suffered from low yields. After cyanamide became commercially available in 1965, direct alkylation of cyanamide were carried out under phase transfer catalysis,[110] the simple procedure making it a promising method for industrial applications.



Scheme 1.23 Synthesis of disubstitued cyanamide from calcium cyanamide

However, this method was only applicable to disubstituted cyanamide synthesis, since monoalkylated cyanamides are more nucleophilic and acidic than cyanamide, thus making it difficult to stop the reaction at monoalkylation stage. As an exception to this, Sharpless reported the synthesis of monoalkylated cyanamide by the treatment of cyanamide potassium salt with tosylate in toluene at 90 ^{o}C (Scheme 1.24).[111]

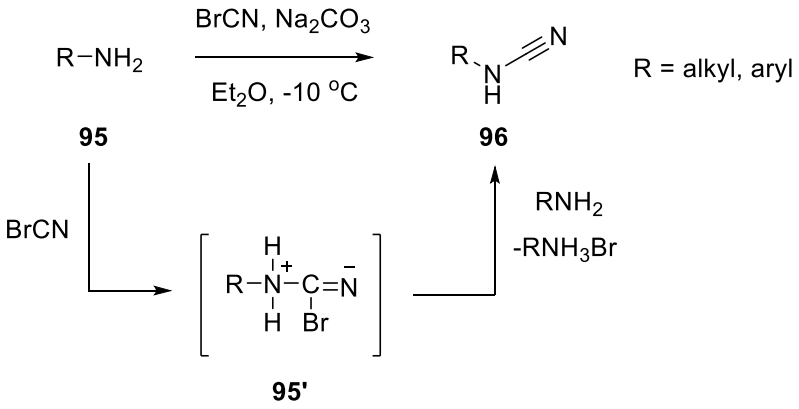


Scheme 1.24 Synthesis of mono-substituted cyanamide from potassium cyanamide

Cyanation of amines

The most commonly used reagent for electrophilic cyanation is cyanogen bromide (BrCN). Cyanogen bromide is toxic and must be handled with caution. The reaction of cyanation of amines follows the addition-elimination pattern, wherein the first stage is the addition of cyanogen bromide to the amino group with the formation of a resonance stabilised cation (**95'**).

The latter is more electrophilic than cyanogen bromide, and it reacts with a second amine molecule giving the corresponding ammonium salt and monosubstituted cyanamide (**96**). It was first reported by Harrison and colleagues[112] in 1976, and has been widely used since[113,114] (Scheme 1.25). Secondary amines also follow a similar pattern giving a disubstituted cyanamide and ammonium salt.

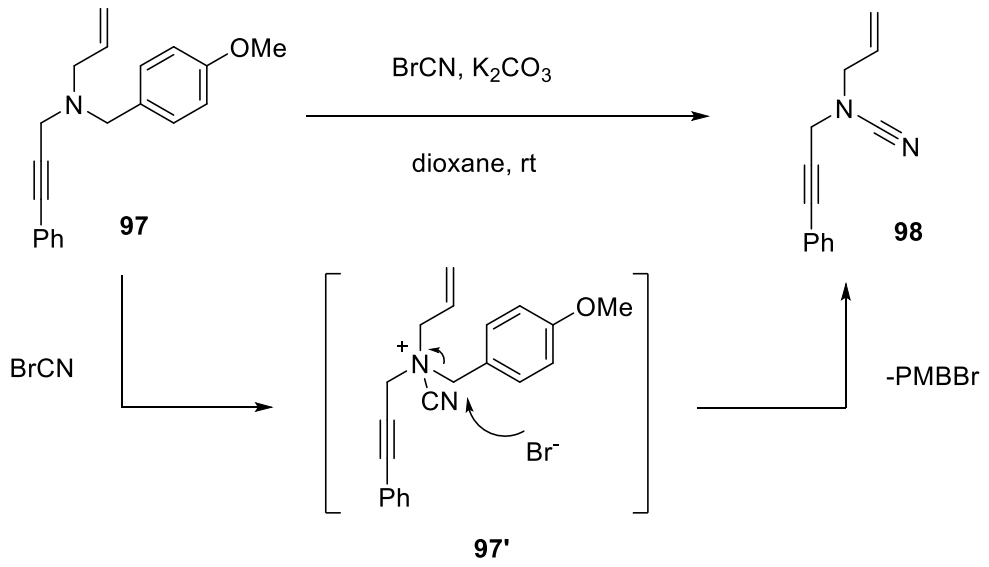


Scheme 1.25 Harrison's methodology for the cyanation of primary amines.

The ammonium salt formed are capable of reacting with cyanamide to give guanidine, hence the reactions are performed in cooling conditions along with a hydrogen bromide acceptor like Na_2CO_3 (or DMF, NaOH, etc.) to prevent further reactions of cyanamide.

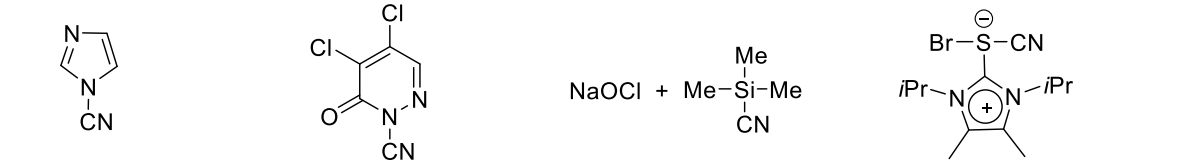
The reaction of tertiary amine with cyanogen bromide was reported in 1900 by Braun, and is called the von Braun reaction.[115] Unlike primary and secondary amines, the reaction of cyanogen bromide with tertiary amines (**97**) takes place through the intermediate formation of *N*-cyanotrialkylammonium bromide (**97'**) which decomposes to disubstituted cyanamide (**98**) and alkyl bromide (Scheme 1.26). Unsymmetrical cyanamide could be obtained with the elimination of a more labile third substituent in the tertiary amine[116] (for eg. Benzyl groups).

Other electrophilic cyanating agents like 1-cyanoimidazole[117] (**99**) and 2-cyanopyridazin-3(2*H*)-one[118] (**100**) have been reported as efficient reagents for cyanamide synthesis (Figure 1.26). However, their preparation involves the use of toxic cyanogen bromide. Recently, an *in situ* generated electrophilic cyanating reagent for disubstituted cyanamides has been developed from bleach and trimethylsilylcyanide (TMSCN),[119] which avoids the use of cyanogen bromide completely. The oxidation of TMSCN (**101**) by bleach is proposed to generate cyanogen chloride *in situ* which reacts with amine to give cyanamides.



Scheme 1.26 The von Braun sequence[116]

Based on the fashion of hypervalent iodine compounds, which are very effective electrophilic group transfer reagents, the concept of hypervalent sulfur compounds was developed by Alcarazo group[120] in 2015. The dihalo (imidazolium) sulfuranes were found to be isolobal to hypervalent iodine species, and also depict the key three centre four electron bond motive. These are readily prepared from thiourea, and give imidazolium thiocyanates in a single step by treatment with TMSCN. The imidazolium thiocyanate (**102**) is a shelf stable, easily scalable compound which was found to be an effective CN^+ synthon for cyanation of both mono and di-substituted amines (Figure 1.26).[120]



99 — 1-cyanoimidazole — *2000*

100 — 2-cyanopyridazin-3(2*H*)-one — *2005*

101 — *in-situ* Cl-CN — *2013*

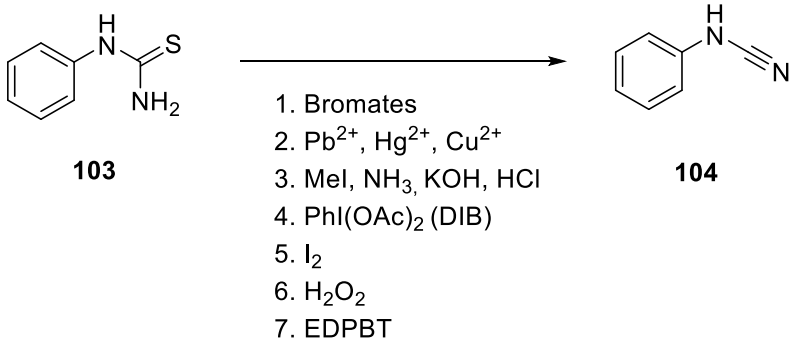
102 — 2-Thiocyanoimidazolium Salts — *2015*

Figure 1.26 Electrophilic cyanating agents for cyanation of amines

Copper-promoted *N*-cyanation of sec-amines was achieved using CuCN by oxidative coupling.[121] The procedure employs O_2 as the oxidant along with CuCN, catalytic $CuBr_2$, TMEDA (*N*,*N*',*N*', *N*'- Tetramethylenediamine) and Na_2SO_4 in CH_3CN, and provides a diverse range of disubstituted cyanamides.

Desulfurisation of thioureas and isothiocyanates

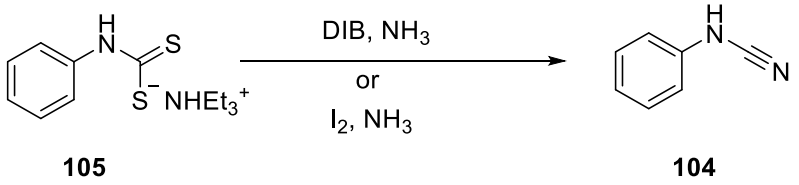
One of the earliest examples for desulfurisation of thioureas by iodate and bromate ions was achieved in 1932.[122] Over the course of years, other oxidative desulfurizing agents like lead acetate,[123] mercury and copper salts,[124] (diacetoxyiodo)benzene (DIB),[125] iodine,[126] hydrogen peroxide,[127] methylating agent (MeI) followed by a basic workup[128] and brominating agent 1,2-ethyllenepyridinium bistribromide (EDPBT)[129] have been used to synthesise mono-substituted cyanamide from thioureas (Scheme 1.27).



103 **104**

Scheme 1.27 Desulfurisation of phenylthiourea using different desulfurizing agents

One pot-conversion of alkyl/ aryl dithiocarbamate salts (obtained by action of CS_2 on amines) to cyanamides has been carried out using DIB and iodine separately in good yields[125,126] (Scheme 1.28). The oxidative desulfurisation of the *in situ* generated thiourea is the key step in the synthesis.

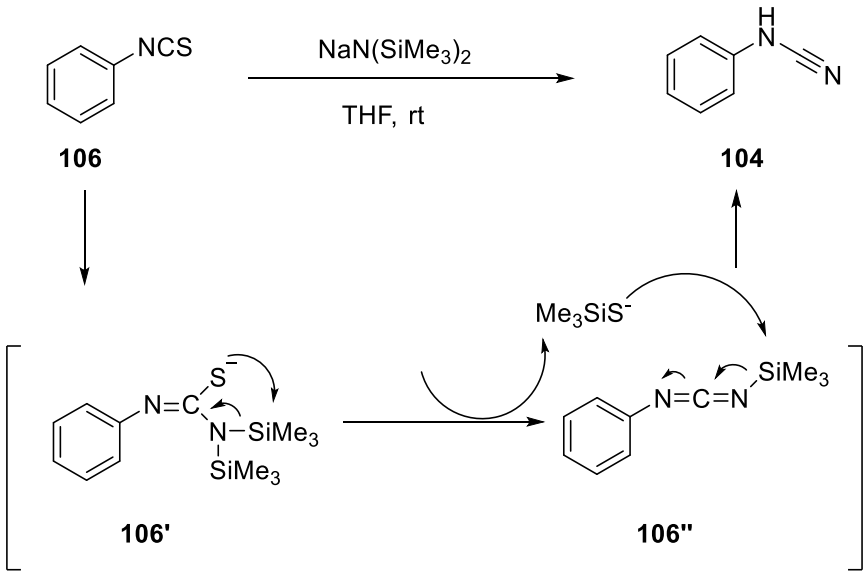


105 **104**

Scheme 1.28 One-pot synthesis of cyanamide from a thiocarbamate salt

Desulfurisation of isothiocyanates (**106**) has been carried out using a strong hindered base like sodium bis(trimethylsilyl) amide $NaN(SiMe_3)_2$.[130] Aliphatic, aromatic, benzoyl and diisothiocyanate were converted into the corresponding cyanamide in good yields. The plausible mechanism proposed by the authors is as depicted in Scheme 1.29. It involves a nucleophilic attack by the base followed by 1,2-elimination to sila-carbodiimide (**106"**), which

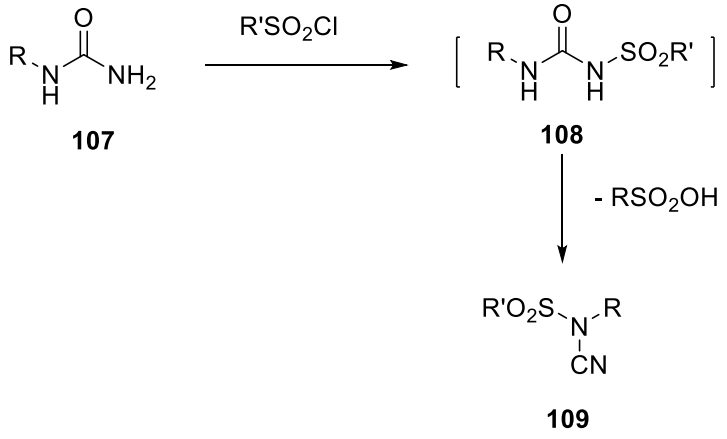
leads to cyanamide upon desilylation (Scheme 1.20). Similarly, deoxygenation of isocyanates[131] using the same base resulted in cyanamides in efficient yields.



Scheme 1.29 One-flask transformation of isothiocyanates to cyanamides

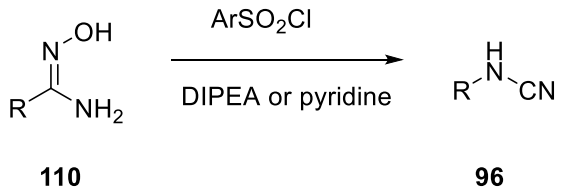
Dehydration of urea and amide oximes (Tiemann Rearrangement)

Reactions involving direct dehydration of urea by the action of arenesulfonyl chlorides in pyridine was first carried out by Kurzer in 1949.[132] It lead to substituted aryl-sulphonyl cyanamides as the main product (Scheme 1.30). It first forms the *N*-aryl-*N*-arylsulfonylurea (**108**) which upon dehydration in presence of arenesulfonyl chlorides yields the sulfonyl cyanamide (**109**) in 50-70% yields.[133]



Scheme 1.30 Dehydration of urea to cyanamide with arenesulfonyl chloride

N-substituted cyanamides were synthesised by the Tiemann rearrangement of amidoximes with benzensulfonyl chlorides and DIPEA (Scheme 1.31).[134] The mechanism was postulated as sulfonylation of the oxime to *O*-sulfonyl amidoxime, which rearranges (Tiemann rearrangement) upon the cleavage of the sulfonyl leaving group to give the *N*-substituted cyanamides in good yields.

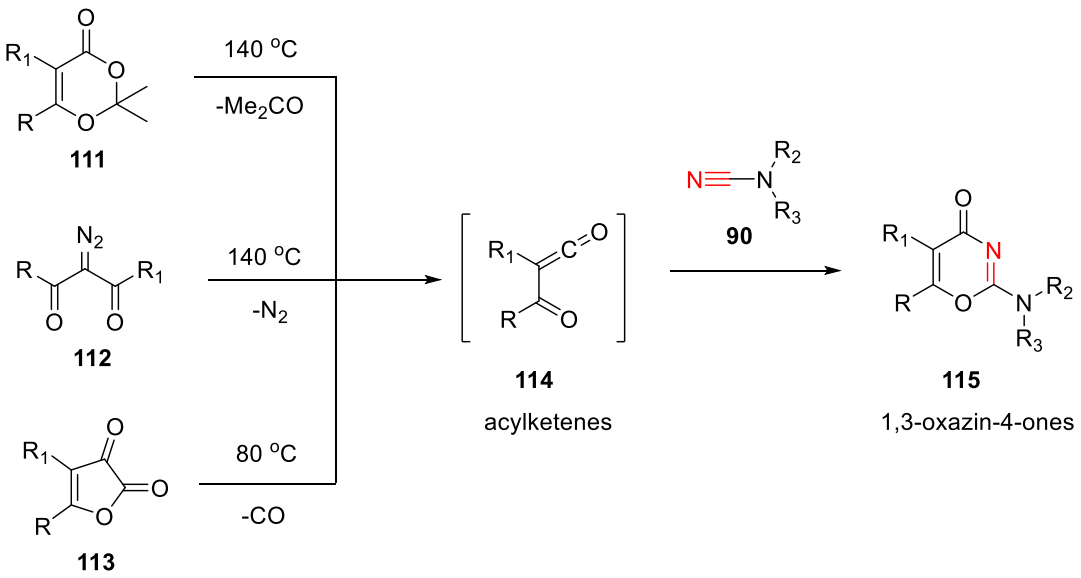


Scheme 1.31 Tiemann rearrangement of amidoximes to cyanamide

1.7.2.2 Cyanamides in the construction of heterocycles

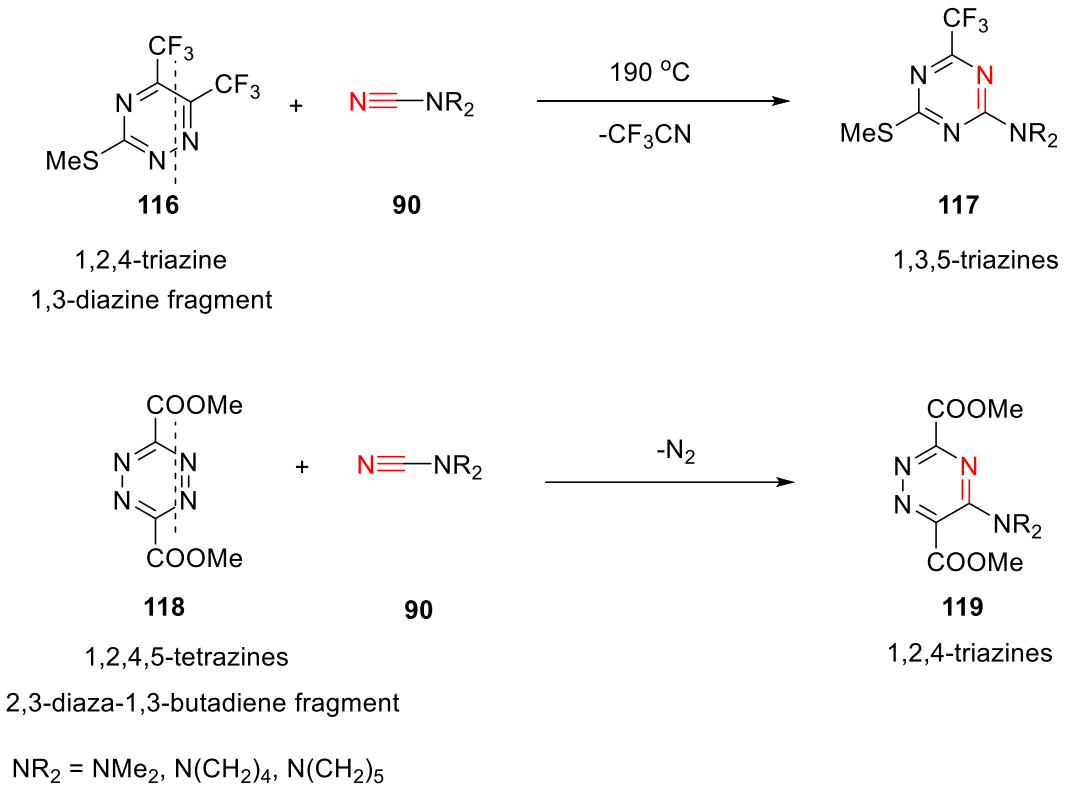
[4+2] cycloaddition

The C≡N bond of the cyanamide acts as a dienophile in [4+2] cycloaddition (hetero Diels-Alder) reactions with 1,3-dienes.[135] One of the examples being the addition of cyanamides (**90**) to acylketenes (**114**) to form 1,3-oxazin-4-ones (**115**).[136] The acylketenes, being unstable are generated *in situ* by thermolysis of their precursors **111-113** (Scheme 1.32).[136–139]



Scheme 1.32 Generation of acyl ketene and its cycloaddition with cyanamide

In contrast to classic Diels-Alder reaction, the [4+2] cycloaddition of cyanamides with dienes involves cycloaddition of electron-rich dienophiles with electron-deficient dienes.[139] This inversion of electronic effects in the addends is observed in almost all the [4+2] cycloaddition of cyanamides.[135]



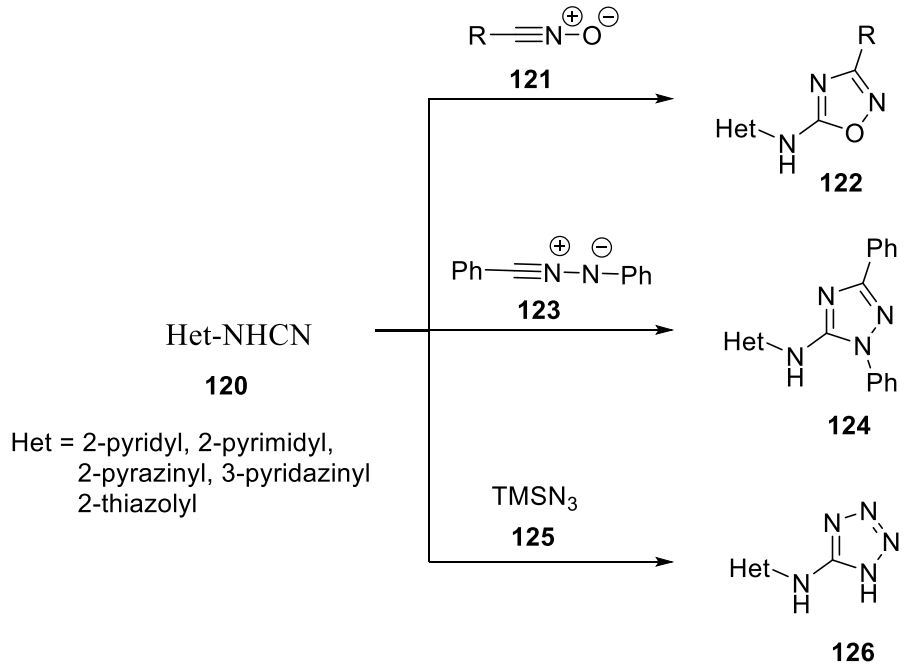
Scheme 1.33 [4+2] cycloaddition of electron-rich cyanamide with electron-deficient dienes

Another example includes the reaction of electron-poor 1,2,4-triazine[140] (**116**) (containing 1,3-diazine fragment) and 1,2,4,5-tetrazines[141] (**118**) (2,3-diaza-1,3-butadiene fragment) with electron-rich *N*-substituted cyanamides to give 1,3,5-triazines (**117**) and 1,,2,4-triazines (**119**) respectively (Scheme 1.33). Thus, these characteristic reactions involving cyanamide are known as reverse diene synthesis (or [4+2] cycloaddition with inversion of electronic effects).

[3+2] cycloaddition

The [3+2] cycloaddition of activated cyano compounds like alkyldicyanamides[142] and heteroaryl cyanamides[143] with various 1,3-dipoles is known in the literature.

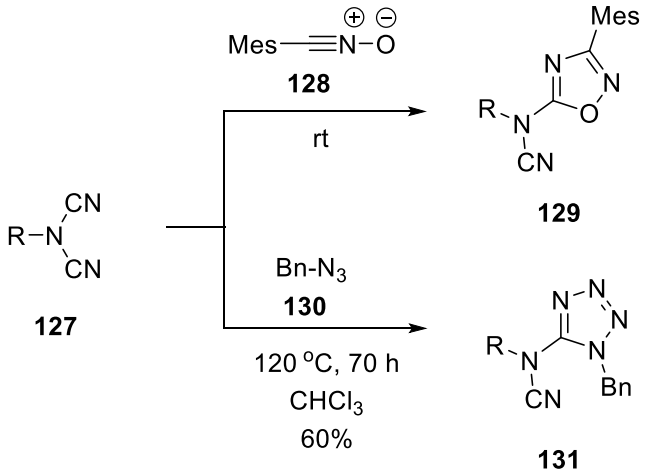
Nitrile oxides, nitrile imines and azides react at the cyano group of the cyanamides in a 1,3-dipolar cycloaddition to give hetarylamino-1,2,4-oxadiazoles (**122**),[144] hetarylamino-1,2,4-triazoles (**124**)[144] and 5-hetarylaminotetrazoles (**126**)[145] (Scheme 1.34).



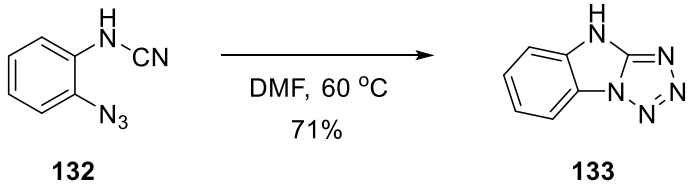
Scheme 1.34 [3+2] cycloaddition of heterocyclic cyanamides with different 1,3-dipoles[142–145]

Dicyanamides react with the 1,3-dipoles nitrile oxide and azide, where the nitrile oxide returned quantitative yields of the oxadiazole product at room temperature, whereas the organic azide required heating for 70 hours for 60% yield (Scheme 1.35).[142]

An intramolecular [3+2] cycloaddition between azides and cyanamides was reported by Sharpless[111] in 2001. The 1,5-fused tetrazoles (**133**) were obtained in quantitative yields for dialkylcyanamides at 140 °C, whereas the monosubstituted arylcyanamides (**132**) returned good yields at just 60 °C (Scheme 1.36).



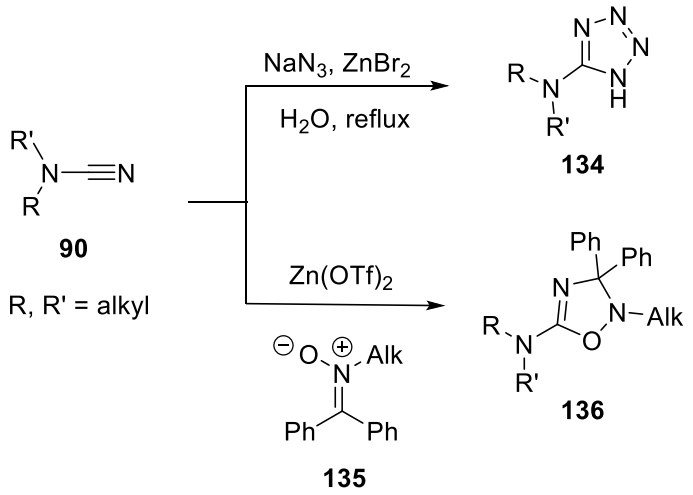
Scheme 1.35 1,3-dipolar cycloaddition of dicyanamide with nitrile oxide and azides[142]



132 **133**

Scheme 1.36 Intramolecular cycloaddition of azidocyanamide (**132**)[111]

Recently, Sharpless demonstrated the cycloaddition of dialkyl cyanamides with azides in water in presence of catalytic zinc salts. The role of zinc proved to be crucial in this cycloaddition as 5-amino tetrazole (**134**) was obtained in good yields [146] (Scheme 1.37).



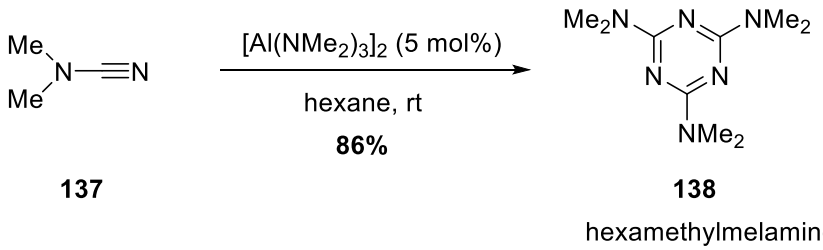
Scheme 1.37 Cycloaddition of dilakylcyanamides with nitrones and azides using zinc catalysts

Alternatively, zeolites like natrolite[147] has been used as a heterogeneous, reusable catalyst for the cycloaddition of azide with aryl cyanamide. The cycloaddition of dialkyl cyanamides with nitrones was carried out by Kukushkin *et al.* using Zn(II)[148] (Scheme 1.37) and platinum ($PtCl_2$)[149] catalysts to give 5-aminosubstituted 2,3-dihydro-1,2,4-oxadiazoles (**136**) in good yields.

Cyclotrimerisation and [2+2+2] cycloaddition

Monosubstituted cyanamides undergo spontaneous cyclotrimerisations to 1,3,5-triazines when stored without particular care or on heating.[133] However, disubstituted cyanamides need activation to participate in cyclotrimerisation, using harsh reagents like triflic anhydride[150] or bis (silyl-substituted)methyl lithium.[151] The antitumour compound hexamethylmelamine (**138**)[152] was prepared by cyclotrimerisation of dimethylcyanamide (**137**) using catalytic

$[Al(NMe_2)_3]_2$ (Scheme 1.38).[153] Mechanistic studies predicted the three insertions of cyanamide into the aluminium-nitrogen bonds followed by nucleophilic ring closure.

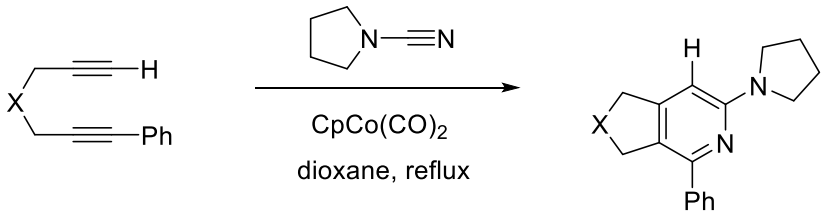


137 **138**

hexamethylmelamine

Scheme 1.38 Aluminium-catalysed cyclotrimerisation of dimethylcyanamide[153]

Cyanamides also participate in [2+2+2] cycloadditions with unsaturated partners. Cobalt-based catalysts[154–156] are the most common catalysts used for this reaction. However, lately, iron[157–159] and iridium-based[160] catalysts have been investigated as well, expanding the scope of these reactions.



139 **140**

X = O, NTs

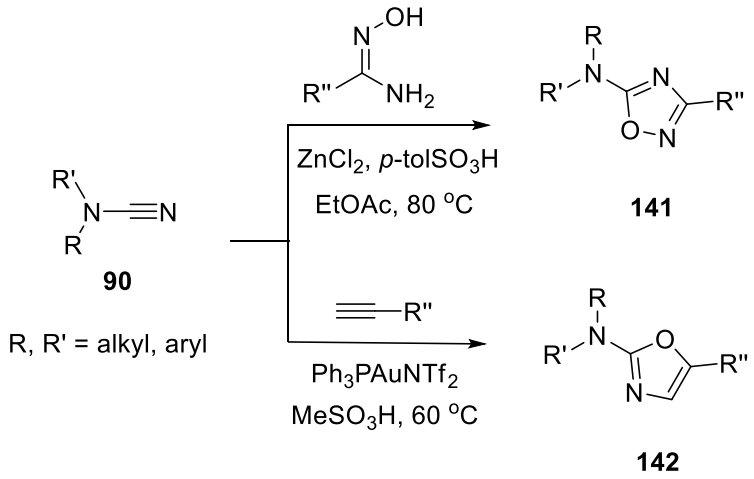
Scheme 1.39 Cobalt-catalysed cycloaddition of a cyanamide and bis-alkyne[156]

The cycloaddition of cyanamides with symmetrical and disymmetrical diynes have been used for the synthesis of 2-aminopyridines, including macrocyclic products.[161] A typical example of substituted 2- aminopyridine (**140**) synthesis obtained by cobalt-catalysed cycloaddition of cyanamide with a bis-alkyne (**139**) is shown in Scheme 1.39.[156]

Metal-catalysed heterocyclisation

Amino-substituted heterocycles have been synthesised by metal-catalysed heterocyclisation of cyanamides with suitable partners like amidoxime[162] and alkynes.[163] The reaction of aliphatic and aromatic amidoximes with the cyanamide **(90)** in the presence of catalytic amounts of $ZnCl_2$ (Kukushkin *et al.*, 2014)[162] gave 5-amino 1,2,4-oxadiazoles (**141**, Scheme 1.40). Whereas this reaction involves the activation of cyanamide, the gold-catalysed heterocyclisation of cyanamides with alkynes[163] does not involve cyanamide activation. The α

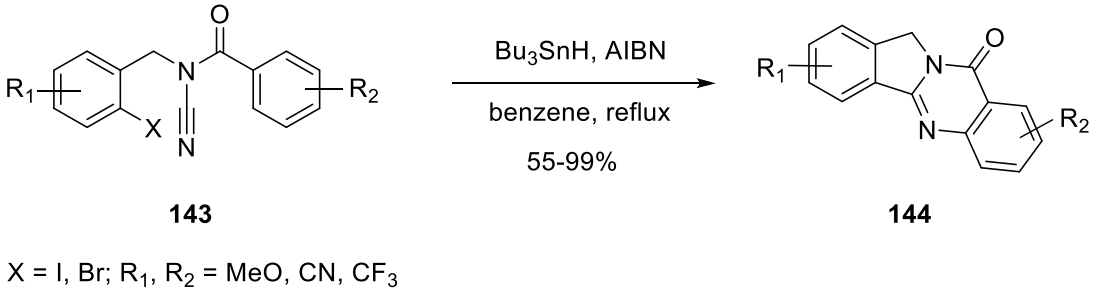
oxo gold carbenes generated *in situ* from the gold activated alkynes and 2-picoline *N*-oxide (oxidant), when trapped with cyanamide gave 2-amino-1,3-oxazoles (**142**) in good to excellent yields with broad substrate scope (Scheme 1.40).



Scheme 1.40 Metal-catalysed heterocyclisation of cyanamides to give aminoheterocycles

Cyanamides as radical partners

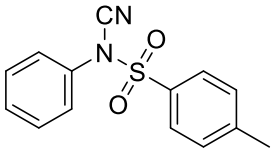
Cyanamides have been used as radical partners for cascade synthesis of polycyclic quinazolines (Scheme 1.41).[164] The bromo- and iodoaryl precursors **143** bearing an *N*-acylcyanamide moiety on treatment with tributyltin hydride and 2,2'-azobis(isobutyronitrile) efficiently underwent the desired radical cascade to **144**. Synthesis of a natural alkaloid luotonin A was developed based on this strategy. Cyanamidyl radical has been recently used as an aminating species for the synthesis of aryl-, heteroaryl primary amines from boronic acids.[165]



Scheme 1.41 Synthesis of polycyclic quinazolines via radical cascades employing cyanamide

N-cyano N-phenyl-p-toluenesulfonamide (NCTS) as a cyanating agent

N-cyano *N*-phenyl-*p*-toluenesulfonamide (**145**) (NCTS) is a bench stable, crystalline solid. It was first synthesised by Kurzer[132] by treatment of *p*-toluenesulfonyl chloride with *N*-phenyl urea in pyridine (Scheme 1.30).



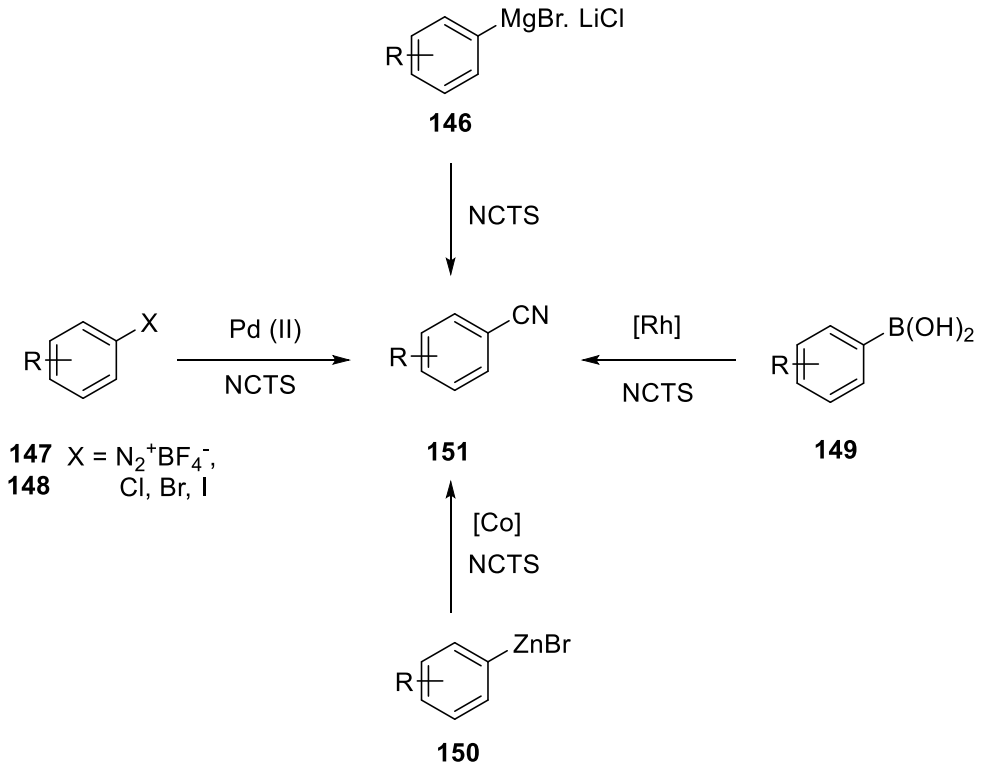
145

Figure 1.27 *N*-cyano *N*-phenyl-*p*-toluenesulfonamide (NCTS)

Since its initial synthesis in 1949, report on the use of NCTS has been very limited. However, in 2011 Beller and colleagues[166] first reported the use of this reagent as a benign cyanating agent which was bench-stable and easy to handle. The bond dissociation energy of N–CN (ca. 497 kJ mol^{-1}) is generally lower compared with C–CN (ca. 555 kJ mol^{-1})[167], favouring its use as a cyanating reagent. Moreover, N–CN bond cleavage of NCTS is believed to be further promoted and activated by both tosyl (Ts) and phenyl groups.[168] Below are the few examples of the use of NCTS as a cyanating agent.

Cross-Coupling of aryl-organometallic/ transition metal reagent with NCTS

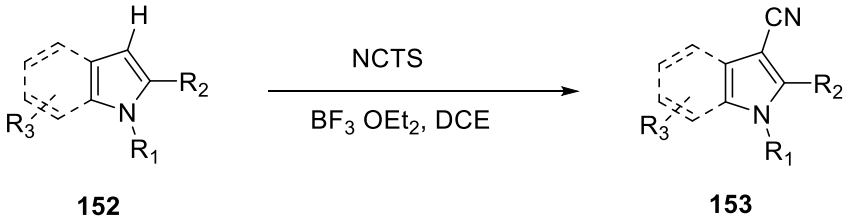
Cyanation of aryl organometallic reagents has been achieved with NCTS as the cyanating agent as illustrated in Scheme 1.42. Functionalised aryl halides[166] (*in situ* generated Grignard reagent) unlike CH activation does not need transition metals, directing groups and high temperature for the cross-coupling reaction with NCTS. Arenediazonium tetrafluoroborates (**147**) and aryl halides (**148**) undergo cyanation utilising Pd(II)/ Ag catalysis system in ethanol,[169] whereas aryl boronic acid (**149**)[170] coupling with NCTS is catalysed by rhodium catalysts (Scheme 1.42). The cyanation of arylzinchalides (**150**)[171] has been accomplished by its reaction with NCTS in presence of cobalt catalysts.



Scheme 1.42 Cyanation of functionalised aryl groups using NCTS as the cyanating agent

C-H activation with NCTS as the cyanating agent

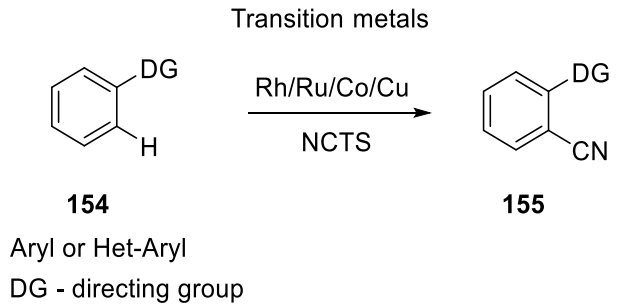
Direct cyanation through C–H bond functionalisation has been found to be an attractive strategy due to the conciseness of the synthetic route without pre-functionalisation.[172] It provides a means for improving the step- and atom-economy in organic synthesis. Wang *et al.* (2011)[173] first reported the C-H activation of indoles using lewis acid as the catalyst, wherein BF_3. Et_2O was used to activate the N-CN bonds in NCTS for the C-3 cyanation of indoles and pyrroles (Scheme 1.43)



Scheme 1.43 Lewis acid-catalysed cyanation of indoles and pyrroles using NCTS[173]

The first use of transition metal for the direct cyanation of aromatic C-H bonds was reported by Yao Fu (2013)[172] using oxime (*O*-methyl oximes) as the directing group (DG) and rhodium

as the catalyst. At the same time, Anbarasan (2013)[174] also carried out a rhodium catalysed cyanation using pyridine as the DG (isoquinoline, benzoquinoline, pyrazine and pyrimidine were also tolerated).



Scheme 1.44 Transition-metal catalysed cyanation by C-H activation using NCTS

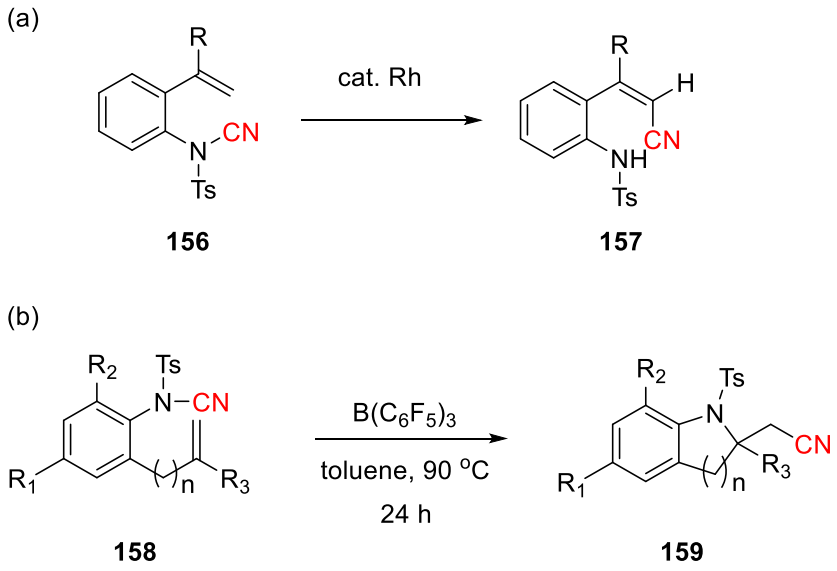
Since then, various directing groups like dialkyl phosphoryl,[175] azo-group (Jie Han *et al.*, 2014),[176] CONHMe group (Wie Yi *et al.*, 2015)[177] and *N*-nitroso (Peipei Sun *et al.*, 2015)[178] have been utilised for the cyanation of arenes and heteroarenes using Rh (III) as the metal catalyst and NCTS as the cyanating agent. The use of Rhodium has also been extended to the cyanation of indoles[179] (C-2 cyanation with pyrimidine as DG), C-7 cyanation for indolines[180] with pivaloyl group as DG. Vinylic C-H cyantions was also carried out independently by Anbarasan *et al.*[181] and Wei Su *et al.*[182] who used pyridine and amides/oximes as the directing group respectively.

Ruthenium-catalysed cyanation have been carried out recently using NCTS, as a cheaper alternative. Ackerman (2014)[183] first reported the use of a Ru (II) catalyst for C-H cyanation of arenes and heteroarenes using amide as the directing group. It was followed by a recent report of C-H cyanation using 7-azaindole as the directing group.[184]

Compared to noble metals, first-row transition metals are more earth-abundant, easily available, and inexpensive. As such, their use as catalysts attracts increasing attention, especially for C−H activation reactions.[185] Ackermann *et al.* (2014)[186] and Glorius *et al.* (2014)[185] both carried out CH activation of arenes/Het-arenes using Co (III) carboxylate as the catalyst using pyridine as the directing group. Ackermann has signified the importance of the carboxylate assistance in the catalytic activity of the Cobalt catalyst. In another example, a cobalt catalysed C-C bond cleavage followed by cyanation was carried out in a single step using NCTS as the cyanating agent by Ozkal *et al.* (2015).[187]

Intramolecular cyanation

Rh(I) catalysed intramolecular cyanation of styrene was carried out, wherein the Rh(I) metal is responsible for the N-CN bond cleavage as well as the C (sp^2) H activation, which gives the product **157** in good to excellent yields (Scheme 1.45a).[188]

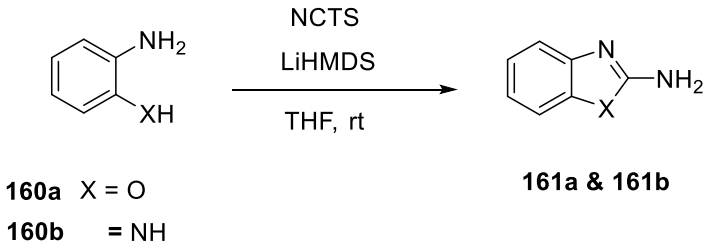


Scheme 1.45 Intramolecular cyanation and amino-cyanation of alkenes

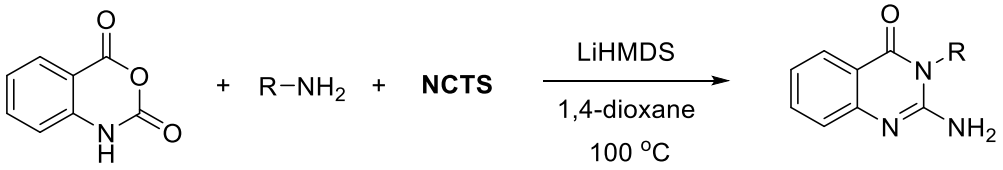
Intramolecular aminocyanation of alkenes followed by cyclisation to synthesise indolines and tetrahydroquinolines using lewis acid [189] (Scheme 1.45b) and palladium/boron catalysts [190] have also been carried out separately.

NCTS in heterocycle synthesis

NCTS has been further exploited for the synthesis of heterocycles. The reaction of NCTS with variously substituted aminophenols **160a** and benzene-1,2-diamines **160b** gave 2-aminobenzoxazoles (**161a**) and 2-aminobenzimidazoles (**161b**) respectively (Scheme 1.46).[191]



Scheme 1.46 Synthesis of 2-aminobenzoxazoles and 2-aminobenzimidazole using NCTS



162 **95** **145** **163**

Scheme 1.47 One-pot synthesis of 2-amino quinazolin-4(3*H*)-one using MCR strategy

A novel multicomponent reaction (MCR) was developed by Raghunadh *et al.*[192] for the synthesis of 2-amino 3-substituted quinazolinone derivatives from isatoic anhydride, amine and NCTS (Scheme 1.47).

1.7.3 Conclusion

The utilisation of *N*-substituted cyanamides in the construction of heterocyclic molecules has seen a rise in the past two decades, contributing a novel route towards heterocycle synthesis.

A review of the cycloaddition reactions of the cyanamide (as described above) shows a major trend towards the utilisation of the nitrile group as a dipolarophile or reacting group in heterocycle synthesis. The reaction leads to an amino-substituted heterocycle in which the nitrile group forms a part of the heterocyclic ring, whereas the amide group RR'N remains intact as the amino substituent of corresponding heterocycle. It should be noted that the concurrent utilisation of both the amino and the nitrile segments of cyanamide has not yet been realised and remains unexplored. We envisaged that exploring this untapped area of cyanamide chemistry could be a new strategy towards heterocycle synthesis.

1.8 Goal: Developing novel strategies for heterocycle synthesis using cyanamide chemistry

Drug resistance has become a burden on public health, social, political and global economies. Recovery time is longer; imposing further stress on the patient, longer hospitalisation and the chance of spreading disease is even higher.[193] As a result, available treatments against infections and tumours diminished, calling for more specific and sophisticated drugs.[193,194] Medicinal chemists are constantly trying to optimise the process of drug discovery by offering alternative procedures for lead hit identification.[67,195,196] However, these processes have proven to be expensive, challenging and time-consuming.

Traditionally, drug discovery involves identification of small bioactive molecules through high-throughput screening of compound collections (libraries) which involve either phenotypic

screening or biochemical assays.[197,198] The success of such a screening endeavor inherently depends on the nature of the compounds forming the collection (libraries). In cases of well-defined biological targets, the structure of a known natural ligand or knowledge of the target structure binding site is used to define the library compounds.[199] Collections are also based on different derivatives of bioactive natural products. However, when the precise nature of the biological target is not known, a rational compound selection process is clearly not possible. In such cases, libraries produced by combinatorial type methods, which involve thousands to millions of compounds are screened to identify bioactive molecules against different isolated biological targets.[199,200]

Most of the existing collection of compounds (libraries) are comprised of large numbers of structurally similar compounds. A general consensus has emerged that library size is not everything; library diversity, in terms of molecular structure and thus function, is crucial.[196–198,201] The lack of structural diversity along with poor physicochemical properties in the commercial compound libraries have caused the current drug discovery process to slow down and more dependent on serendipitous observations.

Heterocyclic structures play an integral part in the drug discovery due to their favourable characteristics (as described in section 1.2). Thus, in the present scenario, devising new strategies to generate libraries of molecules consisting of structurally diverse heterocyclic cores could contribute towards providing a solution to boost the stagnant drug discovery programs.

Moreover, the synthesis of heterocycles is plagued by harsh conditions, prolonged reaction times and laborious procedures[202] rendering such protocols less likely to be incorporated into a drug discovery program. Thus, versatile, efficient and high yielding reactions which avoid multi-step protocols are required. These problems could be overcome using the cyanamide chemistry, where the accessibility of the NCN linkage in a single moiety could lead to heterocycles in single-step protocols in an efficient manner.

Moreover, the utilisation of the dual functionalities (nucleophilic amine and electrophilic nitrile centres) of the cyanamide in heterocycle synthesis, can provide a new route towards generation of diverse heterocyclic cores. In principle, a large library of compounds could be built by making use of few cyanamide derivatives and its cycloaddition with various 1,3-dipoles.

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Chapter-2

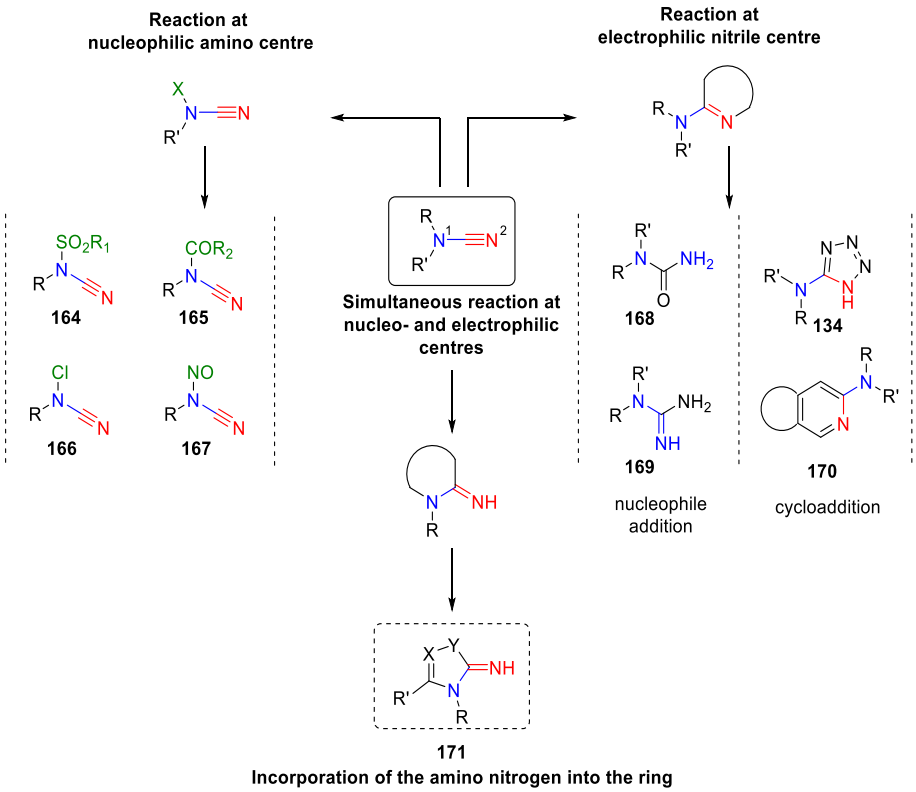
Cyanamides and their reaction with dipoles

Chapter 2

Cyanamides and their reaction with dipoles

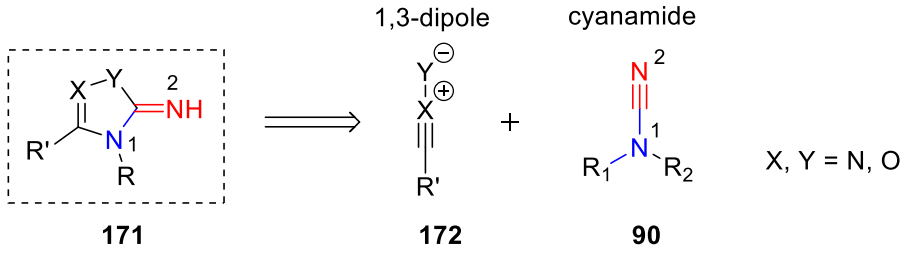
2.1 Hypothesis

Cyanamides feature a Nitrogen-Carbon-Nitrogen (NCN) connectivity, which could provide an important framework for the construction of nitrogen-rich scaffolds. Also, the unique duality of cyanamides, which contain both electrophilic and nucleophilic centres has not yet been fully exploited. Report by Oballa *et al.*[1] reveals enhanced electrophilicity at the nitrile centre of the cyanamide, due to the unshared pair of electrons of the adjacent amino group, as supported by their density functional theory calculations. On the other hand the nucleophilicty of the amino-*N* is reduced due to the conjugation of its unshared pair of electrons with the carbon-nitrogen triple bond. The reactivity of both these centres has been individually explored in a variety of reactions. As depicted in scheme 2.1, reactions at the nitrile group mainly involve nucleophile additions such as addition of water and amines to the cyanamides lead to substituted urea (**168**)[2] and guanidine (**169**) [3–5] respectively which are important building block



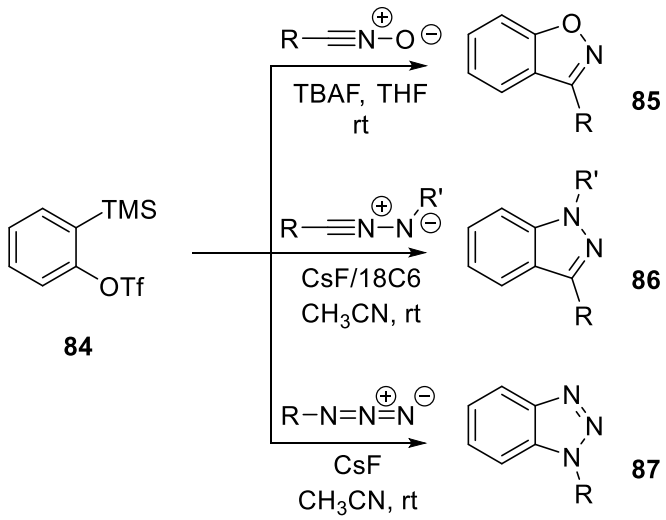
Scheme 2.1 Explored and un-explored avenues of *N*-substituted cyanamide in synthesis

in organic synthesis. The reactions like, acylation of cyanamides take place at the amino group giving *N*-acyl and *N*-sulfonyl cyanamides[6] (**164**, **165**). Like secondary amines, monosubstituted cyanamides undergo nitrosation and halogenation reactions at the amino centre.[7,8] However, a concomitant utilisation of both the reactions centres has not been thoroughly investigated. We envisaged that harnessing the intrinsic electro- and nucleophilic duality of cyanamides simultaneously could be utilised towards the construction of cyclic systems. This can be achieved by reacting with complimentary reactive partners like 1,3-dipoles **172** (eg. nitrile oxide and nitrile imine) as illustrated in Scheme 2.2. The present method would incorporate the cyanamide *N*1- nitrogen atom directly into the core of the ring while the nitrile (-CN2) forming the exocyclic imine, giving heterocyclic molecules like 1,2,4-oxadiazol-imines and 1,2,4-triazol-3-imines.



Scheme 2.2 Retrosynthetic analysis of the hypothesised new heterocyclic system

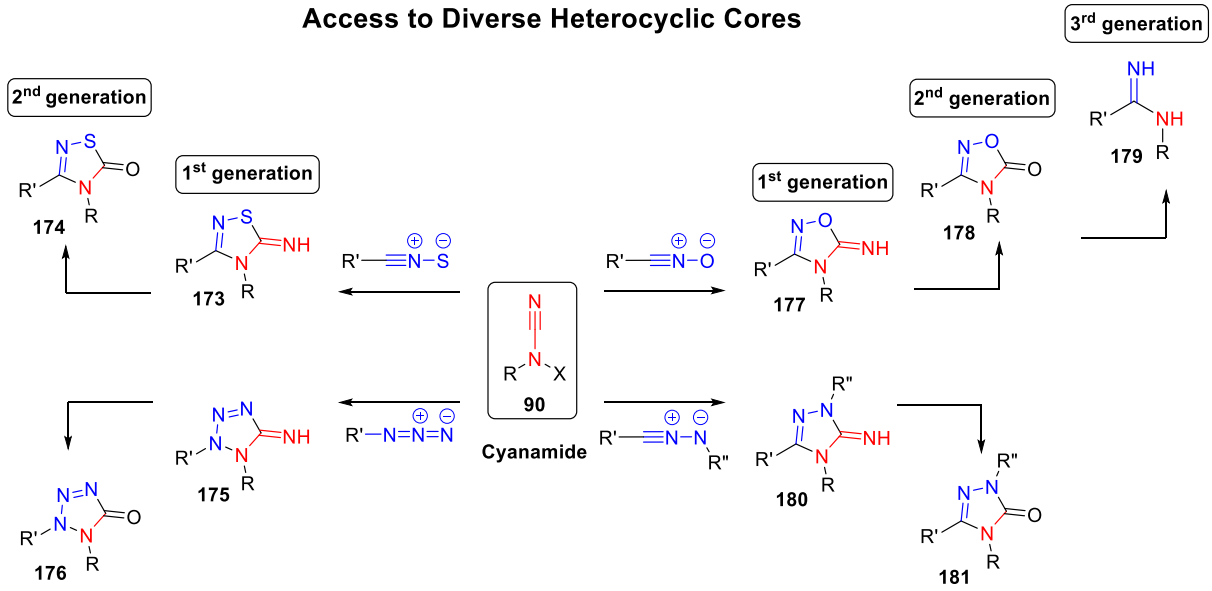
1,3-dipoles like nitrile oxide, nitrile imine, nitrile sulfides and azides have very rich history and has been widely utilised for the synthesis of a variety of heterocyclic cores (section **1.6.2**, Ch-1). For example, the recent work from Moses[9,10] and Larock's groups[11] investigates the



Scheme 2.3 Utilisation of 1,3-dipoles in cycloaddition

utilisation of these reactive species towards the synthesis of benzisoxazole, indazole and benzotriazole with *in situ* generated benzyne under one-pot methodology (Scheme 2.3).

Development of a method where the NCN linkage of the cyanamides can be incorporated as a three atom-two centre dipolarophile like species, would give access to a number of novel heterocyclic scaffolds (Scheme 2.4). Further postfunctionalisation of these 1st generation scaffolds would lead to structurally diverse 2nd and 3rd generation scaffolds, which could help in creating a diverse collection (library) of molecules. Thus the concept of utilising cyanamide in: a 'single-reagent—diverse-scaffolds' strategy for generating a diverse library of compounds, avoiding unfavourable multi-step transformations offered a particularly attractive prospect for investigation.



Scheme 2.4 Proposed use of cyanamide for construction of diverse heterocyclic cores

Figure 2.1 illustrates a number of drugs comprising 1,2,4-oxadiazol-5(4*H*)-imines[12] (**177**), 1,2,4-oxadiazol-5(4*H*)-one (**178**), amidine (**179**) and 1,2,4-triazol-3-imine [13] (**180**) cores that could be readily realised starting from cyanamide like **90** and complementary dipoles like nitrile oxide and nitrile imine. In addition, cores such as oxadiazol-5(4*H*)-one (**178**) also serve as a useful precursor and protecting group for amidines,[14] carboxylic acid[15] and amide[16] bioisosteres. 1,2,4-oxadiazole-5(4*H*)-ones have also been used as prodrugs for anti-thrombosis[17] and peroxisome proliferator-activated (PPAR) delta receptor agonists indicated in the treatment of fatty acid metabolism and glucose utilisation disorders.[18] 1,2,4-oxadiazolones have been previously synthesised from amidoximes by condensation with ethyl chloroformate,[19] pentafluorobenzoylchloride,[20] phosgene;[21] by action of DCC with

phenylimino-triphenyl-phosphoran followed by acid hydrolysis[22] and triphosgene-mediated cyclisation with hydrazido alcohols.[23] The acid hydrolysis of 1,2,4-oxadiazole-5(4*H*)-imines (**177**) provides a new route for the synthesis of 1,2,4-oxadiazol-5(4*H*)-ones (**178**).

Amidines (**179**) are pharmaceutically important cores,[24,25] which have been indicated as potential agents for the treatment of Alzheimer's disease,[26] malaria,[27] parasitic diseases,[28] neurological disorders, [29] platelet aggregation [30] and as serine protease inhibitors.[31] They have also been utilised as useful precursors for the synthesis of various heterocyclic structures like quinazolines,[32] pyrimidines,[33] triazoles [34] and benzimidazoles.[35] Apart from the traditional methods[36-38] used, amidines have been recently synthesised by palladium(II)-catalysed 1,2-carbopalladtion of cyanamides with aryltrifluoroborates[39] and in another instance, aryl carboxylic acids. [40]

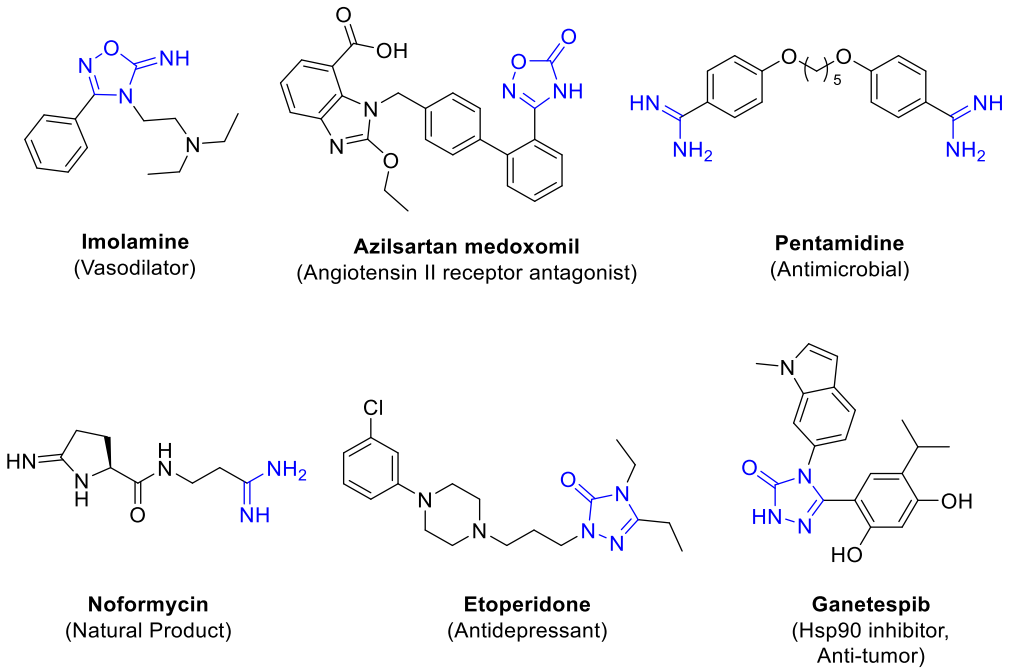
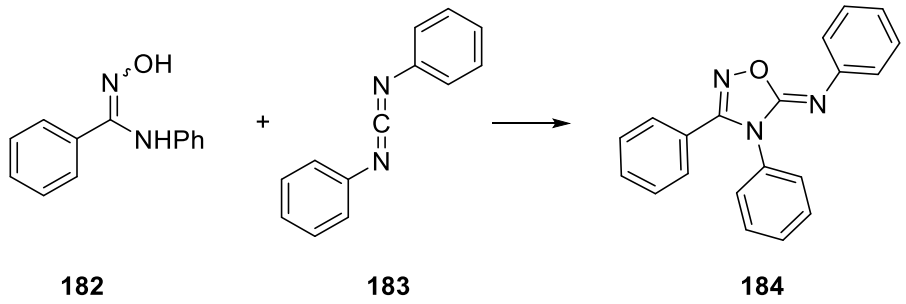


Figure 2.1 Representative examples of clinically important oxadiazolimine, oxadiazolone, triazolone and amidine containing pharmaceuticals

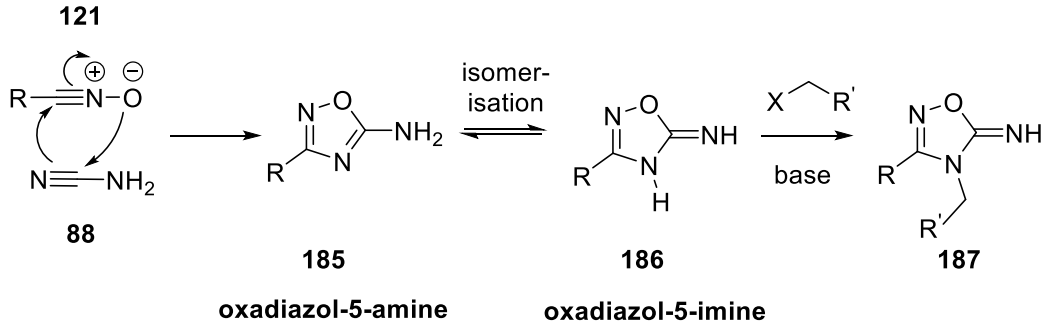
There are very limited examples of cycloaddition protocols to the target cores, and these are mostly restricted to the use of symmetric carbodiimide substrates, leading to the *N*-aryl substituted products. In 1958, Partridge *et al.* first documented an isolated example of *N*-3,4-triphenyl-1,2,4-oxadiazol-5(4*H*)-imine (**184**) synthesis from *N*,*N'*-diphenyl cabodiimides (**183**) and *N*-hydroxybenzamidine[41] (**182**) (Scheme 2.5). Later Huisgen reported[42] a two-step

protocol to 1,2,4-oxadiazol-5(4*H*)-imine involving carbodiimide and triphenyl iminophosphorane.



Scheme 2.5 Partridge synthesis of *N*-3,4-triphenyl-1,2,4-oxadiazol-5(4*H*)-imine

The only known method of making a 1,2,4-oxadiazol-5(4*H*)-imine core was reported by Steren *et al.* in a patent literature.[43] The stepwise method included a 1,3-dipolar cycloaddition of cyanamide (NH_2CN) with nitrile oxide (**121**) to the 1,2,4-oxadiazole-5-amine (**185**), followed by isomerisation and an alkylation to yield the target imine product **187** (Scheme 2.6).

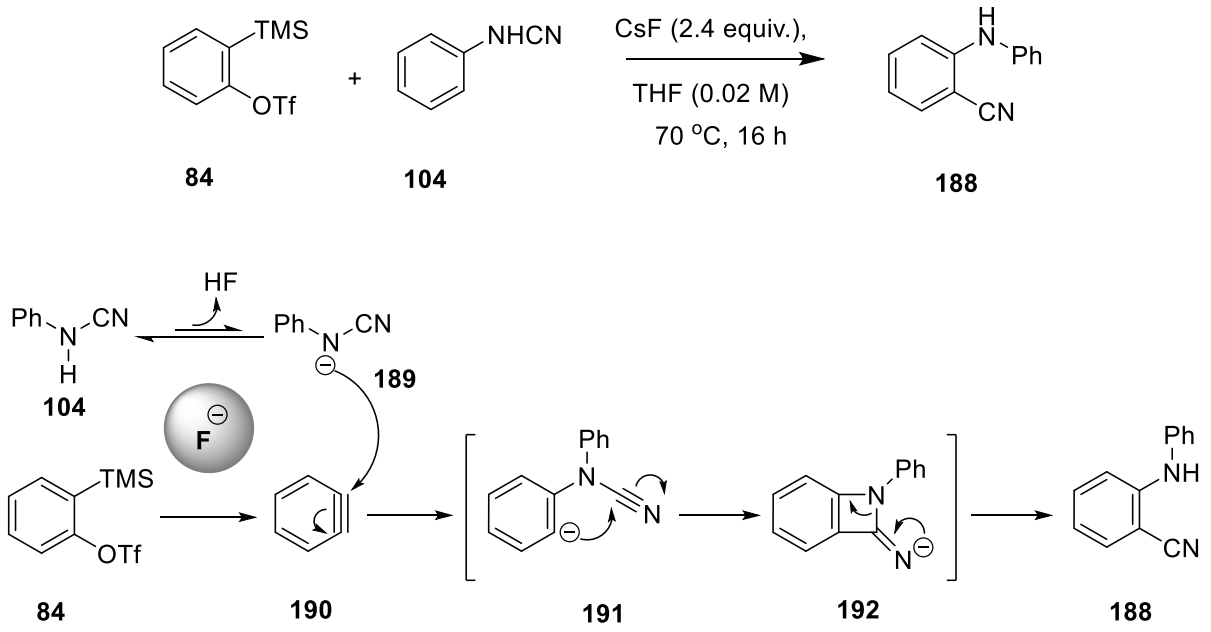


Scheme 2.6 Steren synthesis of 1,2,4-oxadiazol-5(4*H*)-imine

The key challenge to our hypothesis was the identification of appropriately substituted cyanamide derivatives that could participate in reaction with dipoles under mild and benign conditions. Alternatively, a precursor that could generate an anionic species, like $[RNCN]^-$, with enhanced reactivity at the nucleophilic amino centre would be ideally suited.

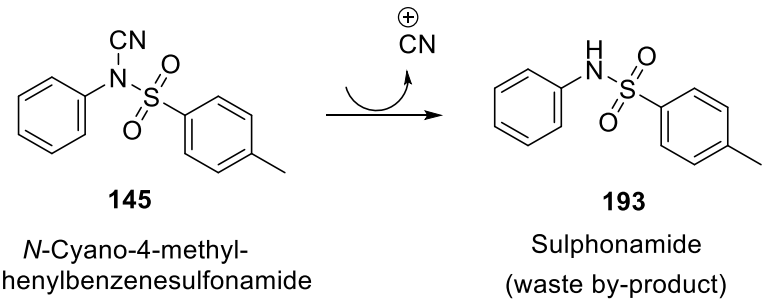
During the early investigation towards a suitable cyanamide substrate and its reactivity, Zeng *et al.* reported the amino cyanation of benzyne **190** on reaction with phenyl cyanamide (**104**) (Scheme 2.7).[44] The reaction offered support to our hypothesis on the simultaneous utilisation of the electrophilic and nucleophilic centre to engage in a ring formation. Here, due to the intrinsic strain of the four membered ring **192** ultimately led to the cleavage of the N-CN bond to offer the amino cyanated final product **188**. Though *N*-phenyl cyanamide (**104**) participated

in the reaction fairly easily, the long reaction time and stability of the starting material is discouraging.



Scheme 2.7 Aminocyanantion of benzyne with phenyl cyanamide

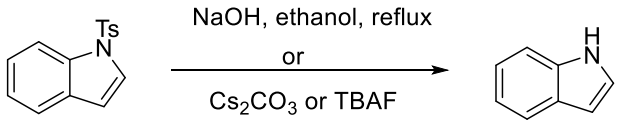
Amongst the other *N*-substituted cyanamides presently studied in literature, *N*-cyano-4-methyl-*N*-phenylbenzenesulfonamide (**145**), also known as NCTS, seemed to be particularly attractive substrate to us. It is a shelf-stable crystalline solid, which can be synthesised easily in a single step from urea. Since its reintroduction by Beller *et al.*, in 2011[45] it has found use as an effective and benign electrophilic cyanating agent. However, its use as cyanating reagent involves the loss of a huge part of the reagent i.e sulphonamide **193** as a waste by-product (Scheme 2.8). Thus, despite its use in a variety of reactions (as discussed in chapter 1), a strategic and atom economic utilisation of the NCN linkage into the core framework of heterocycles is yet to be thoroughly explored.



Scheme 2.8 *N*-Cyano-4-methyl-*N*-phenylbenzenesulfonamide (NCTS) as electrophilic cyanating agent

Further, *N*-cyano-4-methyl-*N*-phenylbenzenesulfonamide (**145**) also offers us an appropriately substituted cyanamide which can be demasked to offer the proposed cyanamide anion $[RNCN]^-$. Sulfonyl functionalities such as benzenesulfonyl, toluenesulfonyl and methylsulfonyl are well documented protecting groups for amino groups, due to their high stability, ease of formation and simple removal.[46] *N*-Desulfonylation is usually accomplished using a variety of methods ranging from- a) dissolving metal reductions (Li or Na) in ammonia, [46] b) single electron transfer reagents like sodium napthalenide,[47a] Na-Hg, *n*-Bu_3SnH; [47b] c) reducing agents like L-Selectride, Red-Al; [46] d) electrolysis; [48] e) photolysis; [49] f) bases like NaOH/KOH (harsh conditions) [50] and Cs_2CO_3 (milder conditions); [51] g) fluoride sources like KF on alumina[52] and tetrabutyl ammonium fluoride (TBAF) [53a-c]. However, the most commonly used methods include the use of base and fluoride sources,[54] which have been widely used for the desulfonylation of *N*-sulfonyl hetero-aromatic compounds as well as *N*-sulfonyl amines (Scheme 2.9 a and 2.9 b).

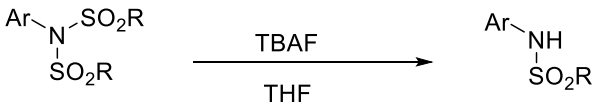
a) Desulfonylation of *N*-sulfonyl hetero-aromatic compounds



194 **195**

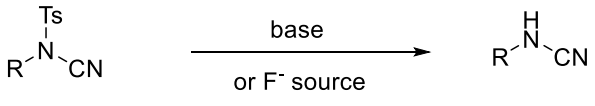
indoles, aza-indoles, imidazoles

b) Desulfonylation of *N*-sulfonylamines



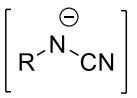
196 **109**

c) Proposed detosylation of *N*-aryl-*N*-tosyl cyanamide



197 **104**

R = alkyl, aryl

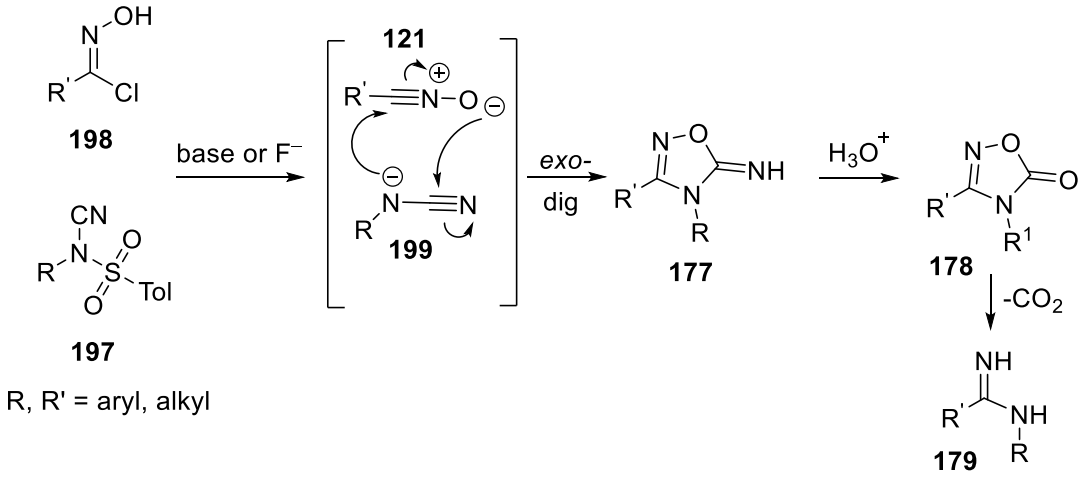


reactive anionic species

Scheme 2.9 Base/Fluoride ion-assisted desulfonylation of *N*-sulfonylamines and proposed detosylation of *N*-aryl/alkyl-*N*-tosyl cyanamide[53a-c]

2.1.1 Coupling of [RNCN]$^{-}$ and nitrile oxide

The known ability of the base/fluoride ions to instigate desulfonylation as well as the easy availability of *N*-sulfonyl cyanamide provided the basis for our hypothesis that base-induced desulfonylation of **197** could generate the reactive cyanamide anionic species [RNCN]$^{-}$ (**199**) (Scheme 2.10). A cyclisative capture reaction of the intermittently generated [RNCN]$^{-}$ (**199**) with dipoles like nitrile oxide (**121**) in an *exo*-dig fashion could deliver a five-membered cycloadduct like 1,2,4-oxadiazol-5(4*H*)-imine (**177**) (Scheme 2.10). Such a cyclisation would be an unprecedented example of a formal 1,3-dipolar cycloaddition between cyanamide ion and nitrile oxide. Further chemical transformations such as hydrolysis and decarboxylation would provide pharmaceutically interesting building blocks such as oxadiazolone[20] **178** and amidine[21] **179**.

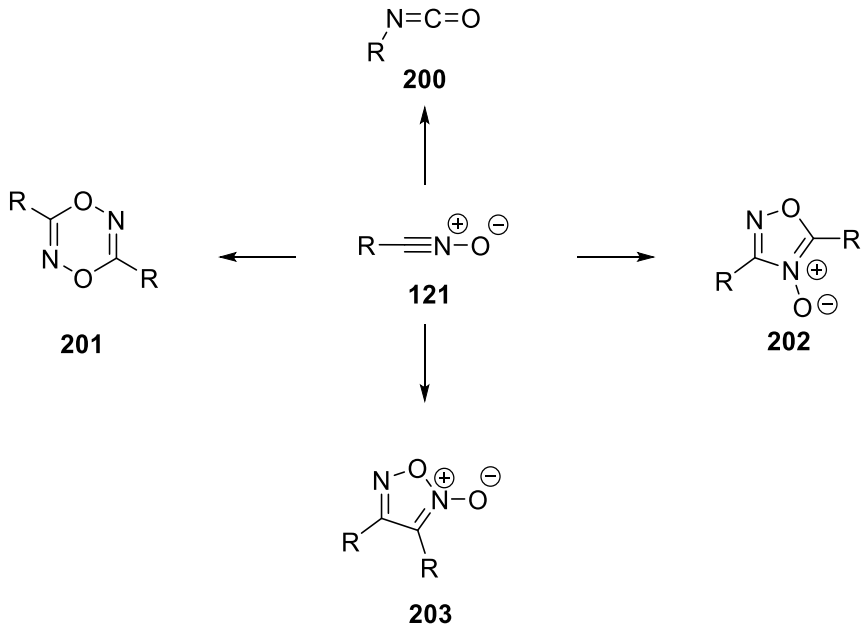


Scheme 2.10 Proposed cyclisative reaction of nitrile oxide **121** with cyanamide intermediate **199** and further transformations

In the development of novel synthetic methods for high throughput synthesis, protocols which are reliable, efficient, precludes the use of too many reagents and generate inoffensive byproducts are quintessential.[55] In this regard an efficient coupling technology of *in situ* generated short lived reactive species utilising single reagent are the best bargain. Hence, it was reasoned that simultaneous generation of both the [RNCN]$^{-}$ and 1,3-dipole (nitrile oxide for instance) coupling partners in a single-pot would offer an attractive prospect towards an efficient and practical outcome. Thus, the reaction of *in situ* generated [RNCN]$^{-}$ and nitrile oxide as a coupling partner was envisaged as the first step towards developing cyanamide as a reagent for generation of diverse heterocyclic structures. NCTS (**145)** was envisioned to be

used as the cyanamide precursor along with hydroximoyl chlorides **198** as the precurosrs for nitrile oxide.

Nitrile oxides 1,3- dipoles[56](**121**) have found wide applications in the synthesis of various heterocycles. Nitrile oxides are routinely generated *via* dehydrohalogenation of hydoximoyl chlorides[57,58] (**198**) either in the presence of appropriate base such as triethylamine (TEA), K_2CO_3, pyridine etc. or fluoride ion using reagents such as TBAF, CsF/18-crown-6 (18-C-6). Unfortunately the chemistry of nitrile oxide is often marred with the high reactivity of the species. Nitrile oxides are known to dimerise in dilute solutions within seconds or minutes[59] to corresponding furoxans[60] (**203**), even at low temperatures (0 ^oC) (Scheme 2.11). Under elevated temperatures, the nitrile oxide isomerise into isocyanates (**200**),[61] whereas in the presence of pyridine in ethanol or excess BF_3 in benzene, self-dimerise into 1,4,2,5-dioxadiazines (**201**).[62] The formation of 1,2,4-oxadiazole 4-oxides (**202**) in the presence of TEA or BF_3 is less significant (Scheme 2.11).[61]



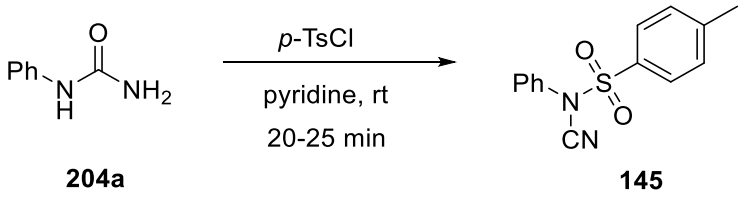
Scheme 2.11 Self reactions of nitrile oxide

In the recent times nitrile oxide has been very efficiently utilised in dipolar cycloaddition reaction wherein in almost all of the cases these reactive species has been generated *in situ* with the complimentary reacting partners. In our present work, to circumvent the problem associated with nitrile oxide reactivity, an *in situ* generation of reacting partners was considered. Hence, detailed studies on the conditions for their generation, stability and reactivity was undertaken.

2.2 Results and Discussion

2.2.1 Synthesis of NCTS

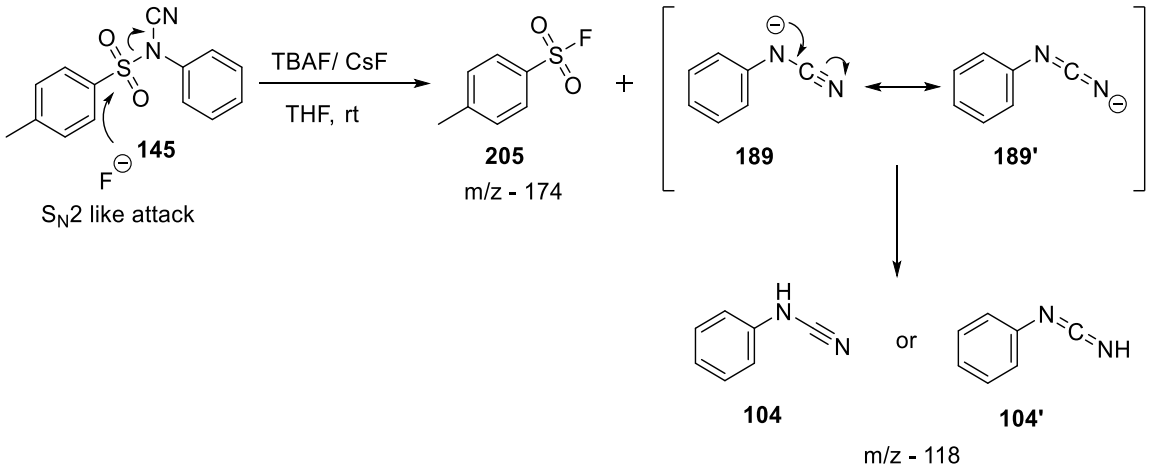
NCTS (**145**) was readily synthesised by the reaction of *N*-phenyl urea (**204a**) with *p*-toluenesulfonyl chloride (*p*-TsCl) in pyridine following literature procedure (Scheme 2.12).[6]



Scheme 2.12 Synthesis of NCTS (**145**) from *N*-phenyl urea

2.2.2 Reactivity of NCTS with different nucleophiles

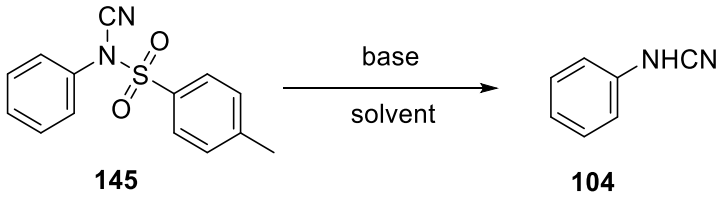
Studies towards the rate of formation of the cyanamide anion from the corresponding precursor under varying reaction conditions were carried out. A number of both fluoride and non-fluoride nucleophiles were screened to instigate the detosylation of NCTS (**145**) as displayed in Table 2.1. Reactions were followed by a combination of TLC and GC-MS analysis.



Scheme 2.13 Products formed by the reaction of fluoride ion with NCTS

The use of ammonium fluoride did not lead to any detosylated product even under heating conditions (entry 1, Table 2.1). Gratifyingly, the use of TBAF resulted in the complete consumption of the starting material forming two new products (TLC) under 5 minutes (entry 2, Table 2.1).

Table 2.1 Screening of NCTS with various nucleophiles



145 **104**

Entry	Nucleophile	Mol Equiv.	Solvent	Temp (°C)	Time	% Conversion[a]
1	NH_4F	1-3	THF/CH_3CN	rt – 50	24 h	--[b]
2	TBAF	1	THF/CH_3CN	rt	5 min	100 %
3	CsF	1	THF	rt	24 h	30 %
4	CsF	2	THF	rt	24 h	70 %
5	CsF	2	THF	50	24 h	90 %[c]
6	CsF	2	CH_3CN	rt	24 h	50 %
7	CsF: 18-C-6 (1:1)	2	THF	rt	4 h	80 %
8	t-BuOK	1	THF	rt	4 h	--[b]
9	t-BuOK	1	THF	50	4 h	100 %

[a] monitored by TLC and GC-MS [b] starting material remains unreacted [c] complex mixture of products formed apart from phenyl cyanamide and tosyl fluoride

GC-MS analysis of the reaction mixture indicated that the two products formed could be *N*-phenyl cyanamide (**104**) or the isomeric carbodiimide (**104'**) with *m/z* 118 and tosyl fluoride (**205**) with *m/z* 174, confirming our hypothesis that TBAF could instigate detosylation of NCTS (Scheme 2.13 and Figure 2.2). Although having similar mass, carbodiimide and cyanamide can be distinguished with IR spectroscopy. Cyanamide[63] shows C-N stretching in the range of 2210-2270 cm^{-1} and the same stretching in carbodiimide[64] is detected at 2100-

2150 cm^{-1}. The formation of phenyl cyanamide (**104**) and tosyl fluoride (**205**) from NCTS is proposed to be initiated by an S_N2 like attack of the fluoride ion on the sulfoxide leading to cleavage of the S-N bond in the NCTS (Scheme 2.13). The tosyl fluoride formed is known to be a highly stable compound, with resistance to reduction,[65] nucleophilic substitution[65] and thermolysis.[66]

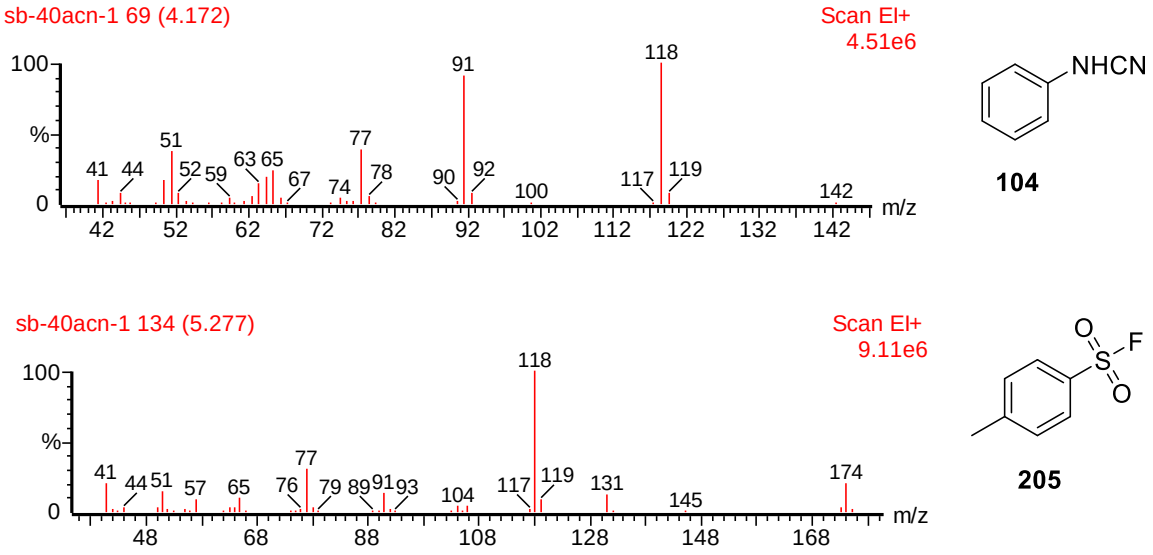
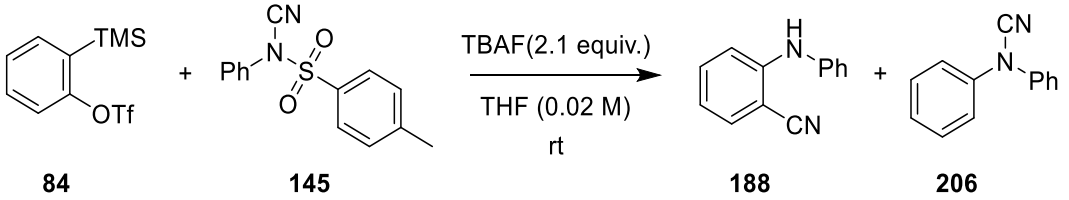
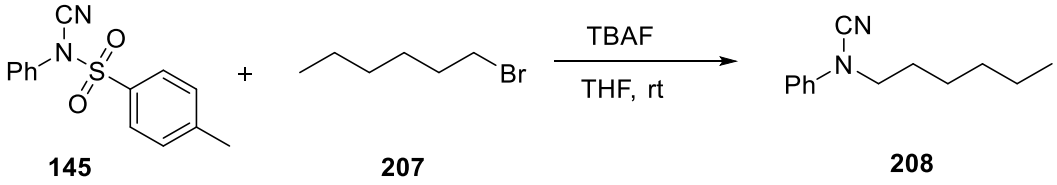


Figure 2.2 GC-MS spectra for the products formed by detosylation of NCTS

A trapping reaction was performed to ascertain the formation of $[RNCN]^-$ anion. NCTS (**145**) was trapped with benzyne (**84**) in presence of TBAF to give a mixture of the amino cyanated product **188** and *N*,*N*-diphenylcyanamide[44] (**206**) indicating the formation of the expected anion intermediate (Scheme 2.14).



Scheme 2.14 Reaction of NCTS with benzyne precursor in presence of TBAF



Scheme 2.15 Reaction of NCTS with hexyl bromide in presence of TBAF

The rate of formation of the reactive cyanamide species $[RNCN]^-$ (**199**) was recorded for other bases under varying reaction conditions. CsF, being a comparatively milder base resulted in slower conversion of the starting material with around 30 % conversion in 24 hours at room temperature (as observed on TLC and GC analysis, entry 3, Table 2.1). Increasing the molar equivalents did result in some improvement with 70 % and 50 % conversion to phenyl cyanamide in THF and CH_3CN respectively (entries 4-5, Table 2.1). The amount of by-product formation was less when the reaction was carried out in acetonitrile compared to THF and most of the cyanamide cleaved to form PhNHCN (**104**). Although the conversion rate is higher in THF, the proportion of PhNHCN is comparatively less as compared to the by-products. When heating conditions were used to accelerate the reaction, it resulted in a complex mixture of products with 50 % conversion to the detosylated product **104** (entry 6, Table 2.1).

Early studies have indicated that the reduced solubility of alkali fluorides in organic solvents[67] are responsible for the low reaction rates. Pederson, in 1967 discovered crown ethers and reported that the anions of the crown ether-metal salt complexes were very reactive in organic solvents.[68] Based on his initial findings, crown ethers were further studied as phase transfer catalysts in reactions involving alkali fluorides.[69]

18-crown-6 is a cyclic ether with a cavity size of 2.6-3.2 A°.[70] The increased solubility and reactivity of KF in organic solvent in the presence of 18-crown-6 was attributed to the complex formation (K^+-18-crown-6) and more availability of the 'naked fluoride' ion.[71] The ability of crown ether to enhance solubility depends on the cavity size, cation radius and the solubility of the metal salt in the organic solvent.[72] 18-crown-6 was found to accommodate the potassium ion (diameter – 2.66 A°) in a 1:1 complex.

However, in a report published by Harpp,[73] CsF:18-crown-6 was also found to increase the reaction rate of a displacement reaction by a factor of 5, inspite of a larger ionic diameter of the Caesium ion (3.4 A°). His report validated Pederson's proposal that the complexes need not be just 1:1 complex to solubilise the fluoride ion, and the CsF-18-crown-6 complex could be a 1:1 edge complex, 2:1 (sandwich) or 3:2 (club-sandwich) complex[70] (Figure 2.3). The complexes with dibenzo-crown-8-CsF gave a similar increase in the reaction rate and the kinetic evidence made the authors conclude that edge (1:1) or sandwich complexes (2:1) have equal or comparative efficiency as with usual or flat 1:1 guest:host ratio complex.[73]

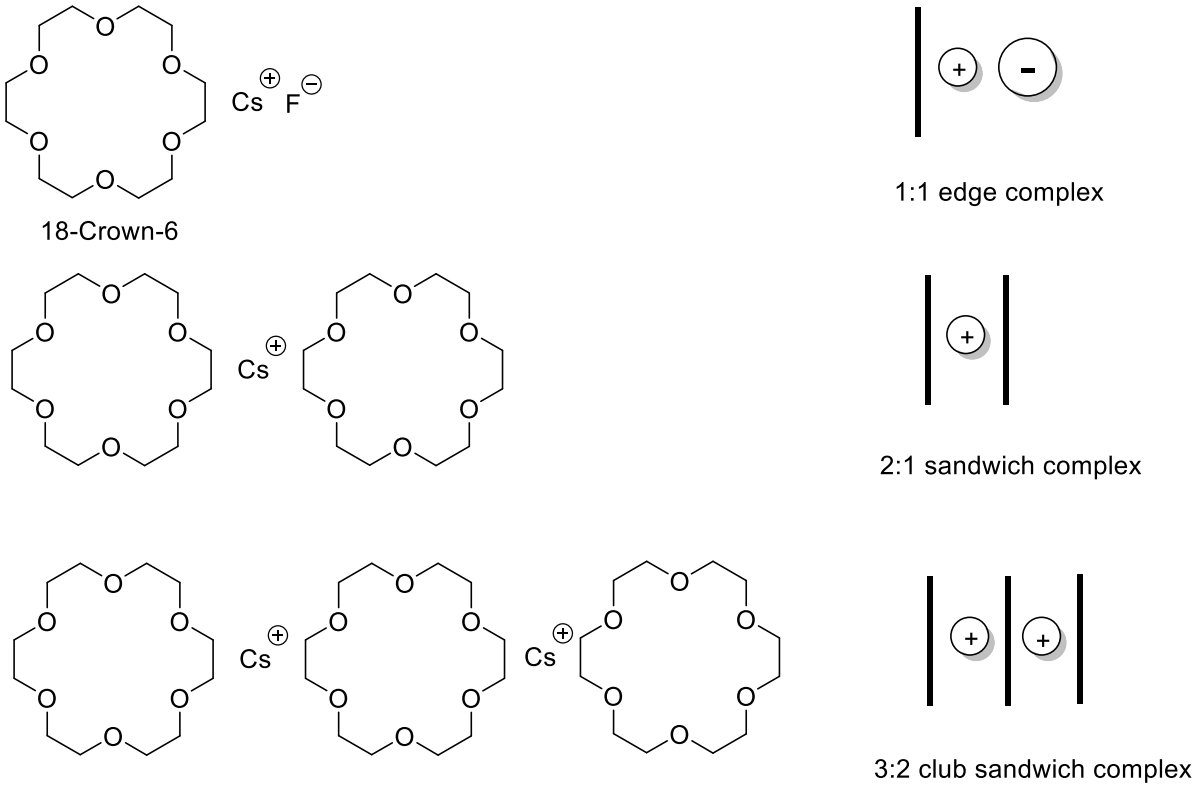
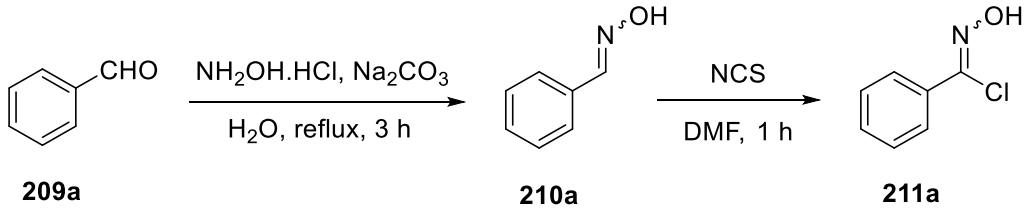


Figure 2.3 Pictorial representation of different possible complexes of CsF:18-crown-6

Recently, Feringa *et al.*[74] and Moses *et al.*[9,10] reported the use of CsF:18-crown-6 complex in 1,3-dipolar cycloaddition reactions with enhanced product yields. Accordingly, when NCTS was reacted with CsF:18-crown-6 in THF, it resulted in around 80% consumption (based on GC-MS analysis) of the starting material in 4 hours (entry 7, Table 2.1)

In presence of ^{t}BuOK as the base, the starting material remained unconsumed at room temperature, but resulted in complete consumption at 50 ^{o}C (entry 8-9, Table 2.1). However, decyanation of NCTS was also observed in this case.

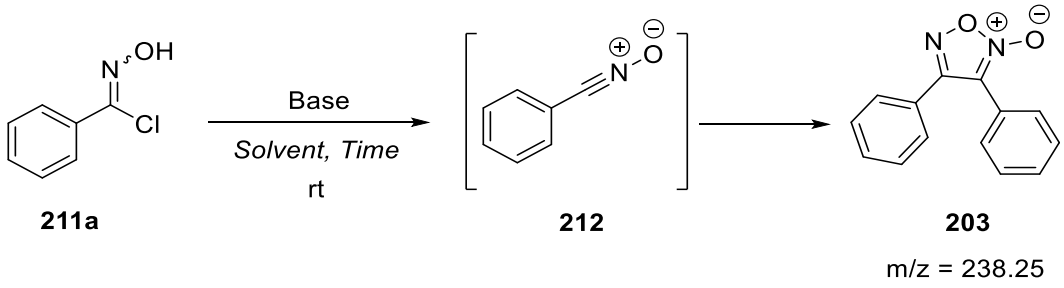
2.2.3 Synthesis of Hydroxymoyl chlorides and generation of nitrile oxide



Scheme 2.16 Synthesis of phenyl hydroximoyl chloride (**211a**)

Phenyl hydroximoyl chloride (**211a**) was prepared in a two-step reaction from benzaldehyde. Benzaldehyde (**209a**) was reacted with hydroxylamine hydrochloride in presence of sodium carbonate as the base, and refluxed in water for 3 hours to get benzaldehyde oxime (**210a**).[75] The use of hydroxylamine in the synthesis of oxime is due to its better nucleophilicity (owing to the alpha-effect)[76] as compared to ammonia. The adjacent α atom (oxygen here) with a lone pair of electrons is responsible for the increased reactivity of the nucleophile. Some of the reasons considered for the increased reactivity are - ground state destabilisation of nucleophiles[77] (repulsion between the electrons of the nucleophilic atom and the α-electrons), transition state stabilisation[78] (on entering the TS, the electron pair on the nucleophile moves away from the nucleus causing a partial positive charge which is stabilised by the adjacent lone pair), increased polarisation of nucleophiles,[79] solvent effect[80] and product stability.[78]

Table 2.2 Screening of bases for the nitrile oxide generation from **211a**



211a **212** **203**

m/z = 238.25

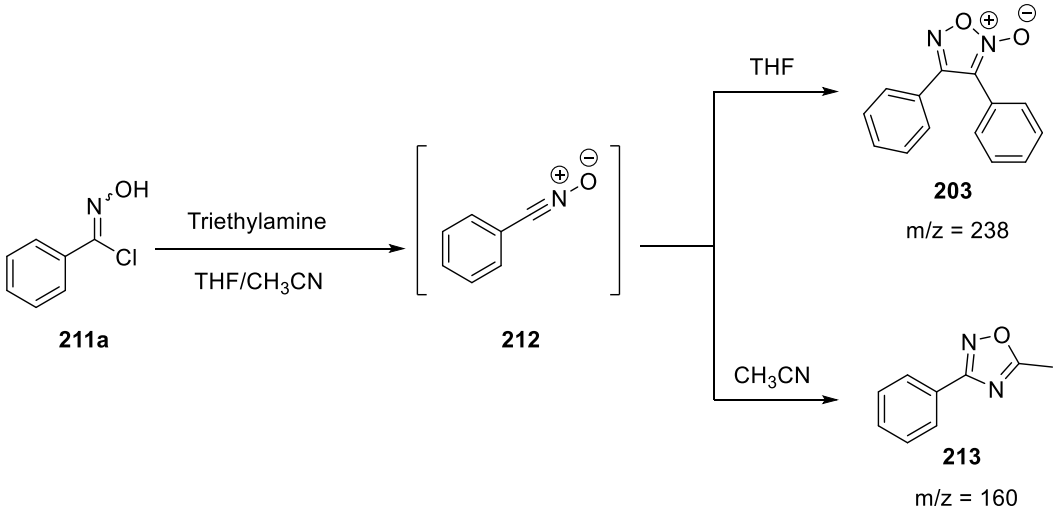
Entry	Base	Mol Equiv.	Time (min)	% Conversion to **203**[a]
1	TEA	2	30	100 %
2	K_2CO_3	2	30	~40 %
3	CsF	2	30	~30 % [b]
4	CsF:18-C-6	2:3	30	50 %
5	CsF:18-C-6	4:6	30	100 %
6	TBAF	1.5	10	100%

[a] analysis by TLC and GC-MS, [b] complete conversion observed in 4 hours

Hudson[81] proposed overlap of doubly occupied p-π orbitals leading to an increase in HOMO energy of the nucleophiles. Studies by Ingold[82] indicate an antibonding HOMO, with a node between the nucleophile and α-atom could be a reason for increased nucleophilicty (ground-state destabilisation). Electronic structure analysis using *Ab initio* calculations[83] of hydroxylamine show that HOMOs of NH_2OH have some antibonding character thereby supporting the Ingold hypothesis to some extent. Thus, the alpha effect can be attributed to the electronic structure of products and their transition state stabilisation, although the precise origin is still inconclusive.

The resultant oxime formed was then reacted with *N*-chlorosuccinimide (NCS) in dimethylformamide (DMF) to give phenyl hydroximoyl chloride (**211a**) after purification by silica gel column chromatography.[84]

When triethylamine (2 mol equiv.) was added to **211a** pre-dissolved in THF, it lead to the formation of nitrile oxide **212**, immediately forming the dimer 3,4-diphenyl furoxan (**203**, Figure 2.3). When acetonitrile was used as the solvent, nitrile group acted as a dipolarophile instead and underwent cycloaddition with nitrile oxide to form 5-methyl-3-phenyl-1,2,4-oxadiazole (**213**) and the furoxan (**203**). The reactions were analysed by GC-MS which showed the corresponding peaks for the oxadiazole (**213**) and **203** (Scheme 2.17).



Scheme 2.17 Different products formed by the reaction of TEA with **211a** in different solvents

When 2 equivalents of K_2CO_3 was added to a reaction flask containing **211a** in THF, the starting material still remained unconsumed after 30 minutes with around 40 % conversion to the dimer (entry 2, Table 2.2). This suggests that the rate of nitrile oxide formation is faster with triethylamine than with potassium carbonate.

The use of CsF (2 mol equiv.) resulted in 30% conversion to the dimer (**203**) in 30 minutes, however the reaction went to completion when kept for 4 hours in the same reaction conditions (entry 3, Table 2.4). Furthermore, to increase the solubility and nucleophilicity of the fluoride ion, 2:3 molar ratio of CsF:18-crown-6 was used which saw 50% conversion to the dimer, however increasing the ratio to 4:6 resulted in complete consumption of the starting material (entry 4-5, Table 2.2).

On reacting the hydroximoyl chloride (**211a**) with TBAF (1 mol equiv.) in THF, the TLC signified no change in the reaction mixture within the 10 minutes, but was later found to be consumed in 1 hour. However, increasing the concentration of TBAF to 1.5 molar equivalents, resulted in complete conversion of the starting material to the dimer (**203**) in 10 minutes (entry 6, Table 2.2).

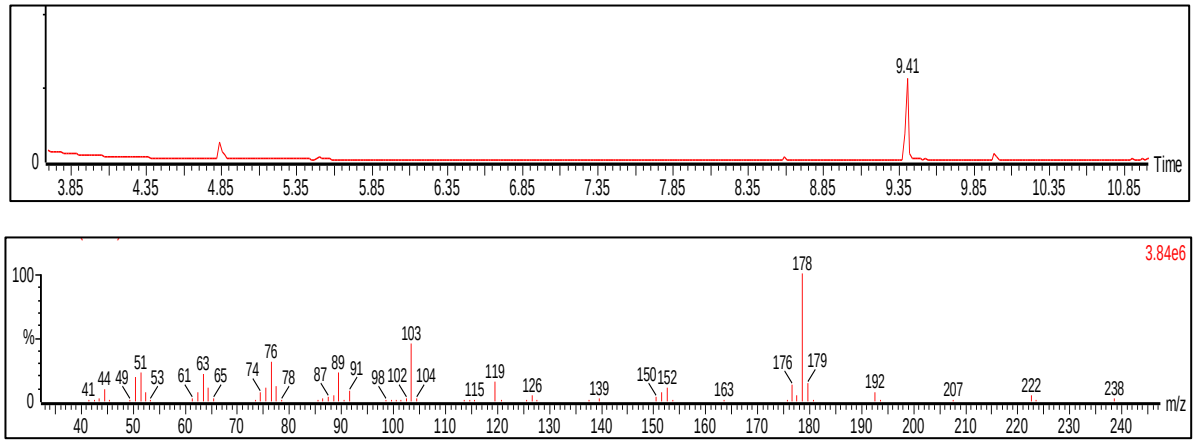
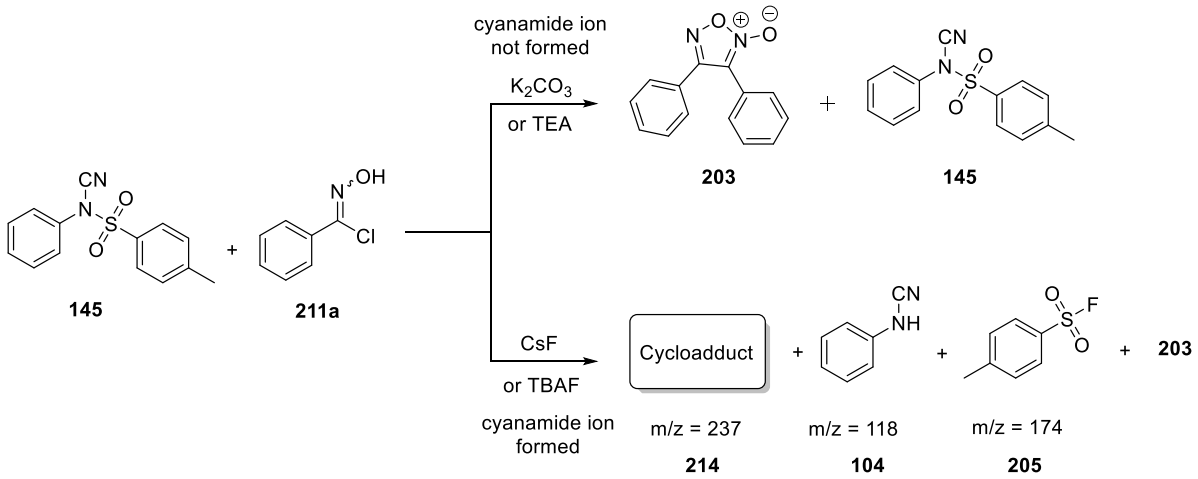


Figure 2.4 GC-MS spectrum for reaction of **211a** with TEA - formation of dimer (**203**)

2.2.4 Optimisation of the cycloaddition reaction of cyanamides with nitrile oxide precursors

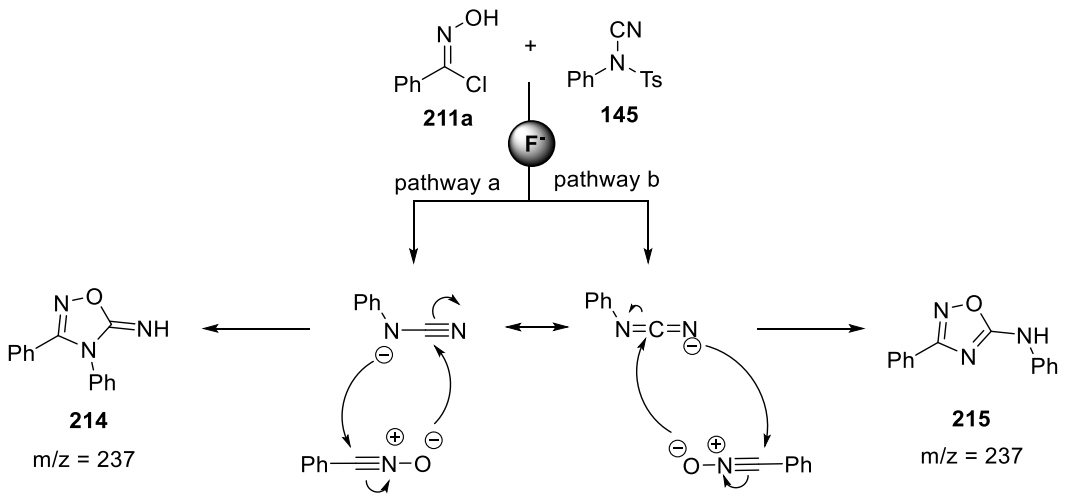
It was conclusive from the studies carried out for the rates of formation of the reactive complimentary species (as discussed in sections **2.2.2** and **2.2.3**), that bases like potassium carbonate and TEA, generate the nitrile oxide (indicated by the dimer formation) but fail to generate the reactive cyanamide species. Whereas, TBAF and CsF were found to generate both the nitrile oxide as well as the $[RNCN]^-$ species (indicated by the detosylation of NCTS **145**) from their corresponding precursors.



Scheme 2.18. Reaction of **211a** and NCTS in presence of various bases

So, accordingly when a mixture of NCTS (**145**) and phenyl hydroximoyl chloride (**211a**) in THF was treated with bases like potassium carbonate and triethylamine, furoxan (**203**) was isolated as an exclusive product along with the unreacted NCTS (entry 1-2, Table 2.3). The nitrile centre of NCTS was found immune to the nitrile oxide in presence of TEA/K_2CO_3, as no cycloaddition product was detected.

However, in the presence of TBAF, formation of a new product **214** was observed, which showed a *m/z* of 237 in GC-MS (Scheme 2.18). The GC-MS also showed peaks corresponding to phenyl cyanamide (**104**), *p*-toluenesulfonyl fluoride (**205**) and the dimer (**203**) indicating the detosylation instigated by the nucleophilic fluoride ion. We reasoned that the reaction can proceed in two ways: through pathway **a** (Scheme 2.19) to give 1,2,4 oxadiazol-imine **214** or through pathway **b** (Scheme 2.19) to give the isomeric heterocycle, 5-amino substituted-1,2,4-oxadiazole **215**. The formation of the isomeric heterocycle was proposed by the reaction of nitrile oxide with carbodiimide ion, which is the tautomeric form of cyanamide ion.



Scheme 2.19 Possible reaction pathways: fluoride ion-mediated reaction of **211a** and NCTS

Preliminary GC-MS study of the reaction indicated that the product is 3,4-diphenyl 1,2,4-oxadiazol-5(4*H*)-imine (**214**) as opposed to (**215**) (see figure 2.5 for fragmentation pattern). The M─43 peak is characteristic for **214** arising from the loss of CHNO species, and formation of the amidine species (*m/z* = 194) (Figure 2.5). The product was further confirmed by IR which showed the characteristic peaks for NH and C=N (exocyclic) at 3288 and 1692 cm^{-1} respectively.

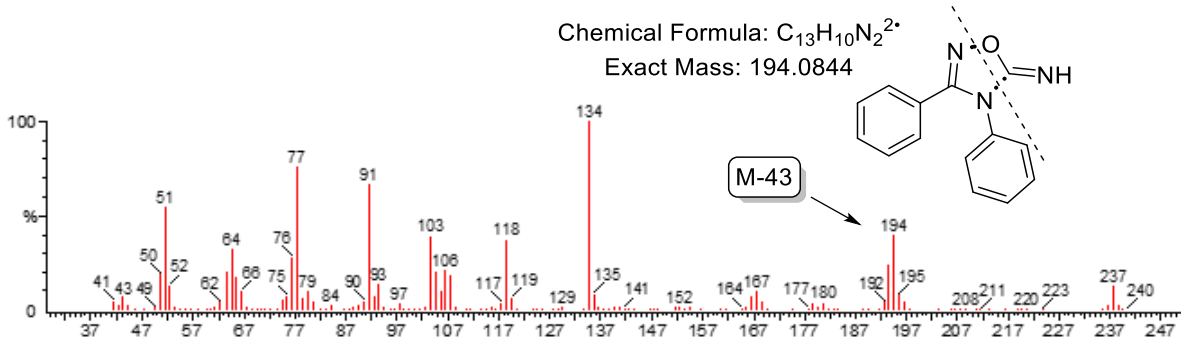
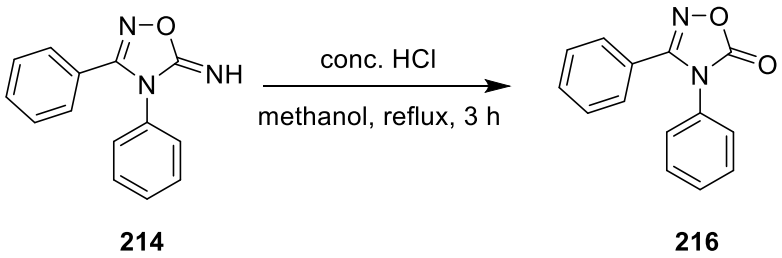


Figure 2.5 Fragmentation pattern for **214** leading to the M-43 peak

The product was further confirmed by NMR analysis (^{1}H, ^{13}C, COSY, HMBC, HMQC). Though the product **214** was solid, all attempt to generate appropriate size crystals for diffraction failed. Later on in our studies the hydrolysed product of the oxadiazol-imine (**214**) to the corresponding oxadiazolone (**216**) (Scheme 2.20) was successfully crystallised and X-ray recorded. The atom-connectivity of **216** was confirmed through single x-ray crystallography (Figure 2.6), which in turn confirmed the formation of **214** in the first place in the reaction between cyanamide and nitrile oxide.



214 **216**

Scheme 2.20 Hydrolysis of oxadiazol-imine to oxadiazolone

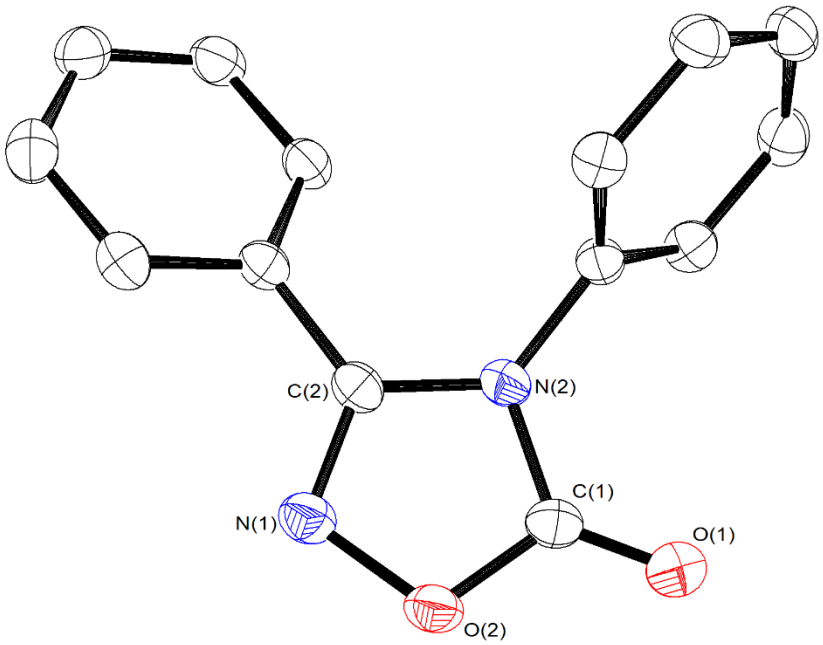
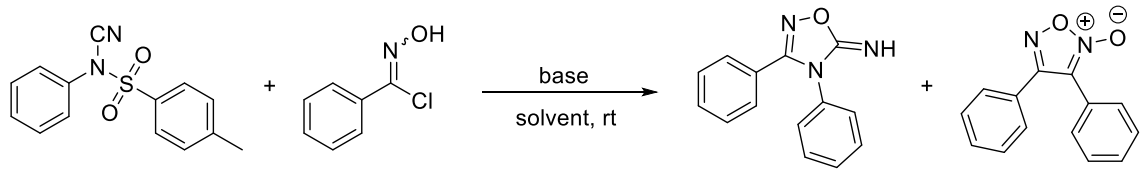


Figure 2.6 ORTEP view of **216**

Once the structure of the major product was established, the TBAF-mediated cycloaddition reaction was explored for further optimisations. The initial screening involved reacting 1 molar equivalent of phenyl hydroximoyl chloride (**211a**) with NCTS (**145**) in presence of 3.4 equivalents of 0.5 M TBAF in THF at room temperature, which resulted in 61 % yield of the cycloadduct (**214**) under 10 minutes. Self-competing reactions like the dimerisation of nitrile oxide and protonation of the cyanamide anion $[NCN]^-$ were also observed along with the desired cycloaddition reaction. Slow addition of TBAF over a period of 20 minutes did not have any significant effect on the yield (59%, entry 7, Table 2.3). Changing the order of addition resulted in a lower yield of 33%, where **211a** was added after 5 minutes to a solution of pre-dissolved NCTS and TBAF in THF (entry 8, Table 2.3).

Table 2.3 Preliminary screening of base/F^- for the cycloaddition reaction



145 1 equiv + **211a** 1 equiv → **214** + **203**

Entry[a]	Base	Molar Equiv.	Solvent[b]	Time	Yield (%)[c]
1	K_2CO_3	2	THF	10 min -24 h	--[d]
2	Et_3N	2	THF	10 min -24 h	--[d]
3	NH_4F	2	THF	10 min -24 h	--[d]
4	TBAF	3.4	THF	10 min	61
5	TBAF	3.4	CH_3CN	10 min	62
6	TBAF	3.4	THF (1 M)	10 min	50
7	TBAF	3.4	THF	20 min[e]	59
8	TBAF	3.4	THF	10 min[f]	33

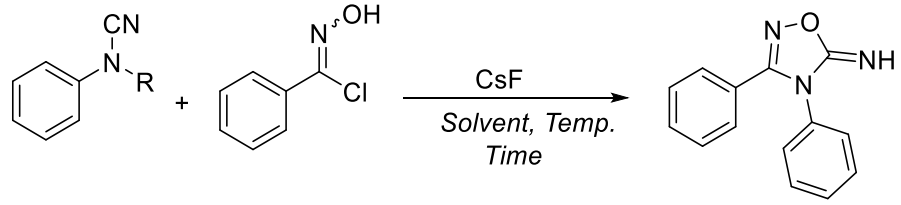
[a] Reactions were performed on 0.64 mmol scale, [b] 0.5 M, [c] Isolated yield, [d] **214** not detected; **145** remained unreacted with **203** detected by TLC only, [e] TBAF added over a period of 20 min, [f] **211a** added after 5 min to a mixture containing **145**, TBAF in THF

Hence, the initial studies indicated towards a fast and unmatched rate of generation of both reactive species in presence of TBAF giving the cycloadduct as a product in 10 minutes. However, a moderate product yield of 61% called for further optimisation studies, in order to decrease the self-competing reactions and get optimum yields. Meanwhile, CsF was explored next as the fluoride source for the cycloaddition reaction.

2.2.5 Reaction optimisation with CsF as the fluoride source

Reacting NCTS (**145**) and phenyl hydroximoyl chloride (**211a**) in the presence of 2.4 molar equivalent of CsF in THF at room temperature yielded no product. Increasing the CsF to 3.4 molar equivalent lead to product formation, albeit in very low yield (15%, entry 2, Table 2.4), whereas heating the reaction mixture only caused a marginal increase in the yield (24 %, entry 3, Table 2.4).

Table 2.4 Reaction screening with CsF as fluoride source



145 R = Ts
104 R = H

211a

214

Entry	Base	Molar Equiv.	Solvent	Temp (°C)	Time	R=Ts Yield (%)[a]	R=H Yield (%)[a]
1	CsF	2.4	THF	rt	4 h	--[b]	--[b]
2	CsF	3.4	THF	rt	>24 h	15	32
3	CsF	3.4	THF	50	4 h	24	40
4	CsF:18-C-6	3.4:3.4	THF	rt	4 h	27	36
5	CsF	6	THF	rt	10 min	38	--[c]
6	CsF	6	CH_3CN	rt	4 h[d]	57	63

[a] Isolated yield, [b] no product formed, [c] not attempted, [d] slow addition of **211a** (in THF) over a period of 1.5 hours

It is known[73] that addition of 18-crown-6 to CsF results in sandwich-type complexation of the Cesium with the 18-crown-6 resulting in the availability of more naked fluoride ion. Using equal amounts of CsF and 18-crown-6 (3.4 mol equiv.) helped in increasing the yield to 27%,

whereas excess CsF (6 mol equiv.) in THF resulted only in 38 % yield of the desired product. In all the cases, competing self-dimerisation reaction of the nitrile oxide was prominent as the nitrile oxide formation rate was found to be comparatively faster than that of the cyanamide $[NCN]^-$ species. Taking this into consideration, NCTS was treated with 6 molar equivalents of CsF, and the phenyl hydroximoyl chloride (**211a**) was added slowly over a period of 1.5 hours with the help of a syringe pump. Slow addition of **211a** helped in increasing the yield to 57% (entry 6, Table 2.4). Using *N*-phenyl cyanamide (**104**) instead of tosyl cyanamide as the dipolarophile substrate gave comparable yields (entries 2-6, Table 2.4). However, similar yields in a few minutes with TBAF render the use of CsF less attractive. Hence, further optimisations were carried out with TBAF as the fluoride source for the nitrile oxide-cyanamide (formal) cycloaddition reaction.

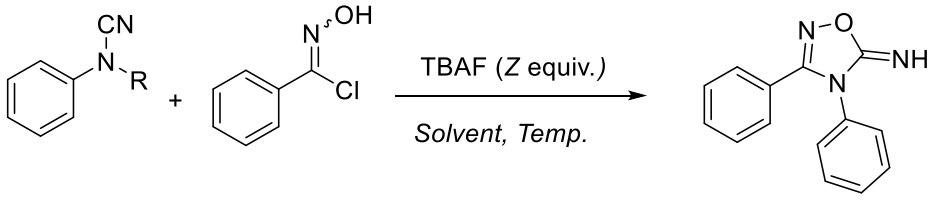
2.2.6 Reaction optimisation with TBAF as fluoride source

The initial reaction with 1 molar equivalent each of the starting material (**211a**) and (**145**) with 3.4 molar equivalents of TBAF yielded the product in 61 % yield in 10 minutes. The molar equivalents of TBAF was reduced to 2.5, which gave the product **214** in similar yields (57%, entry 1, Table 2.5). TLC analysis showed that NCTS was immediately detosylated forming phenyl cyanamide (**104**), with nitrile oxide dimer (**203**) also forming as a by-product. Nucleophilic attack by a fluoride anion is heavily dependent on the counter cation, solvent choice and the extent of hydration.[67b] TBAF is known to form a weak intimate ion pair and it is a good source of "*naked*" fluoride ion in organic media.[85] That would explain the higher nucleophilicty of TBAF (hence faster reaction rates) in comparison to CsF.

The key to the cyclisation reaction was undoubtedly the concomitant generation and subsequent cyclisation of the two highly reactive species. Hence, a systematic investigation into the optimisation studies was conducted by: changing the relative ratios of the substrates; molar equivalents of TBAF and its rate of addition; reaction temperature and the effect of solvent.

The reaction of **211a** and NCTS (1 molar equiv. each) at 0 ^oC in presence of TBAF in THF caused a marginal increase in the yield with 62 % product formation and 12 % of NCTS recovered (entry 2, Table 2.5). However, phenyl cyanamide (**104**) formation was observed after 5 minutes even in ice-cold conditions. This observation lead us to speculate that the ice-conditions slowed down the formation of cyanamide species $[RNCN]^-$.

Table 2.5 Reaction optimisation with TBAF as fluoride source



145 R = Ts
104 R = H

X equiv.

211a

Y equiv.

214

Entry	**145** *X* equiv.	**211a** *Y* equiv.	*Z* equiv.	Solvent	Temp	Time	Yield (%)[a]
1	1	1	2.5	THF	rt	10 min	57
2	1	1	2.5	THF	0 °C	10 min	62
3	1 (**104**)	1	2.5	THF	0 °C	10 min	61
4	1	1.25	3	THF	0 °C	10 min	67
5	1	1.5	3	THF	0 °C	10 min	65
6	1	1.5	3	THF	0 °C	1 h[b]	55
7	1.5	1	3	THF	0 °C	10 min	69
8	1.25	1	3	THF	0 °C	10 min	65
9	**1.25**	**1**	**3**	**THF**	**0 °C**	**1 h[b]**	**79**
10	1.25	1	3	THF[c]	0 °C	1 h[b]	49
11	1.25	1	3	DCM	0 °C	1 h[b]	77

12	1.25	1	3	CH_3CN	0 °C	1 h[b]	76
13	1.25	1	3	Toluene	0 °C	1 h[b]	64
14	1.25	1	3	DMF	0 °C	1 h[b]	58
15	1.25	1	3	1,2-DME	0 °C	1 h[b]	68
16	1.25	1	3	Et_2O	0 °C	1 h[b]	67
17	1.25	1	3	H_2O[d]	rt	24 h	0[e]
18	1.25	1	3	H_2O:acetone (9:1)	rt	24 h	Trace[f]
19	1.25	1	3	H_2O:DMSO (9:1)	rt	24 h	17

[a] Isolated yield [b] addition of TBAF over a period of 1 h by the use of syringe pump, [c] reaction carried out with reagent grade THF in open flask conditions, [d] also performed in phosphate buffer, [e] starting material remain unreacted, [f] crude NMR

Hence, it was hypothesised that reacting the cyanamide with excess of nitrile oxide precursor **211a** would give an optimum product yield as the fast-generating nitrile oxide (in excess) could react with the available cyanamide fully. So, a reaction of 1.25 molar equivalents of **211a** with 1 molar equivalent of NCTS (**145**) in presence of TBAF (3 mol equiv.) at 0 °C was tried (entry 4, Table 2.5), which gave the product **214** in 67 % yield (mild improvement over 61 % yield). Increasing **211a** to 1.5 molar equivalents did not help, neither did the slow addition of TBAF as yields dwindled lower down to 55 % (entry 5-6, Table 2.5).

In each of the above cases, furoxan (**203**) formation was observed (TLC and GC-MS), calling for higher amounts of NCTS to be used in the reaction. It was hypothesised that the reactive cyanamide species in excess would react fully with the nitrile oxide, leading to the exclusive formation of the product **214** with minimum side reactions. Hence, when excess NCTS was used, the cycloadduct (**214**) was obtained in yields ranging from 69-73% (entry 7-8, Table 2.5). Optimal results were obtained using 1 molar equivalent of **211a** and 1.25 molar equivalents of NCTS (**145**) with slow addition of TBAF (3 mol equiv.) over a period of 1 hour at 0 °C, leading to the formation of product in 79 % yield (entry 9, Table 2.5). The slow addition of TBAF was

found to be crucial for the concomitant generation of nitrile oxide **212** and the $[NCN]^-$ species **189**, as the product- 1,2,4 oxadiazol-5 (4*H*)-imine (**214**) was isolated in the best possible yields. The desired cycloadduct **214** was also obtained when reagent grade THF was used in open flask conditions (49%, entry 10, Table 2.5). The hydrolysis of oxadiazol-5-imine (**214**) was observed in this condition as 12% of the oxadiazolone (**216**) was isolated from the reaction mixture.

Next, the solvent effect was studied, wherein polar solvents like DCM and acetonitrile provided a comparative yield to THF, whereas other solvents had deleterious effects (entry 11-16, Table 2.5). To extend the use of this method in biological systems, the reaction was tried in water and phosphate buffer, but the starting materials remained unreacted. However, water: DMSO (9:1) system returned the desired product in a modest 17% yield.

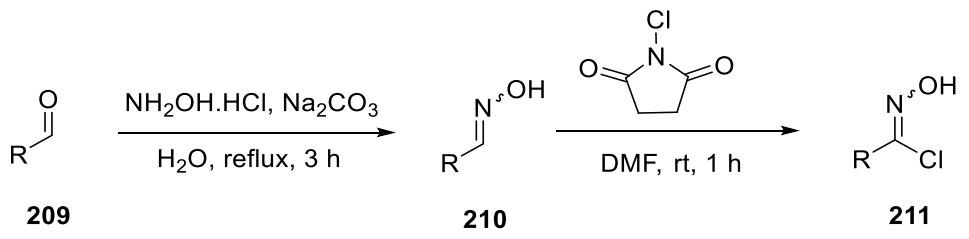
The optimised method presents the first example of one-pot reaction of cyanamide as a dipolarophile like species towards nitrile oxide to render the five-membered oxadiazol-5-imine (**214**) product.

2.3 Substrates scope: Substituted hydroximoyl chlorides and *N*-aryl-*N*-tosyl cyanamides

2.3.1 Synthesis of hydroximoyl chlorides

Once the optimisations were done, we set out to investigate the robustness of the reaction conditions. Thus, a range of aryl hydroximoyl chlorides bearing different substituents including aliphatic, electron-donating and electron-withdrawing groups were synthesised (Figure 2.7).

The hydroximoyl chlorides were prepared in two-steps from aldehydes. The aldehydes were reacted with hydroxylamine hydrochloride in presence of sodium carbonate as the base, and refluxed in water for 3 hours to get aldoximes (**210**).[75] The aldoximes were obtained in excellent yields and were used further without any purification.



209 **210** **211**

Scheme 2.21 Synthesis of hydroximoyl chlorides

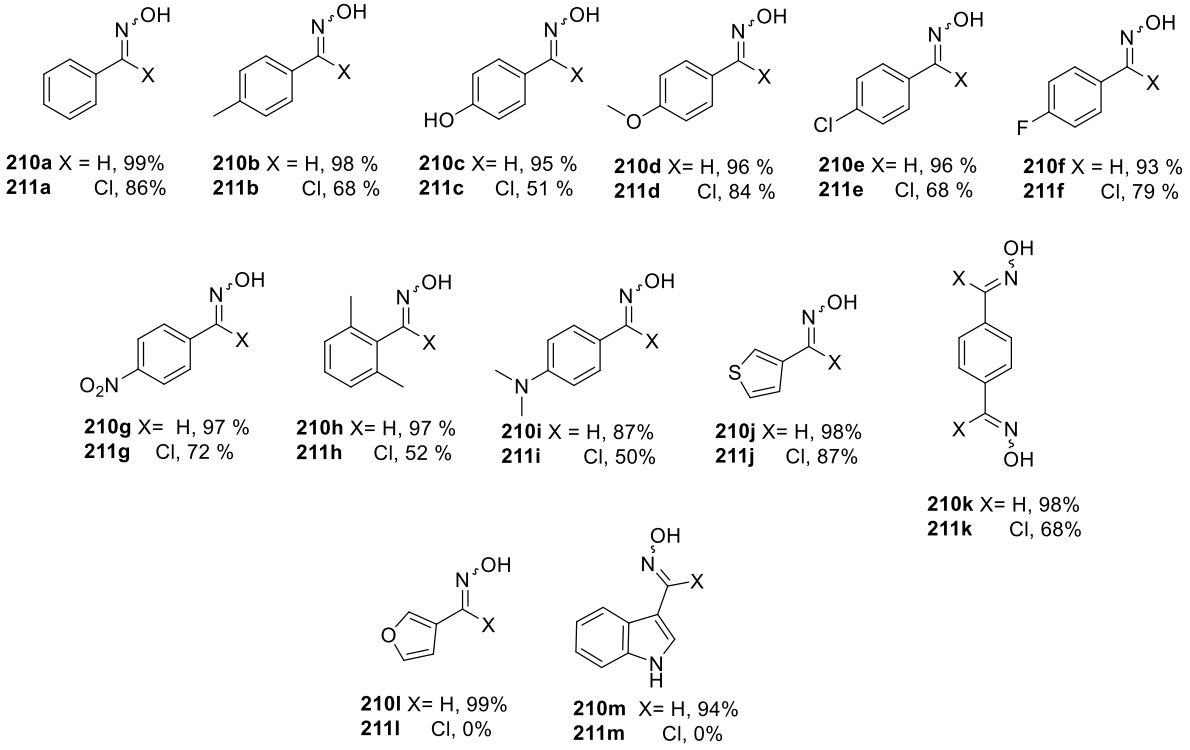
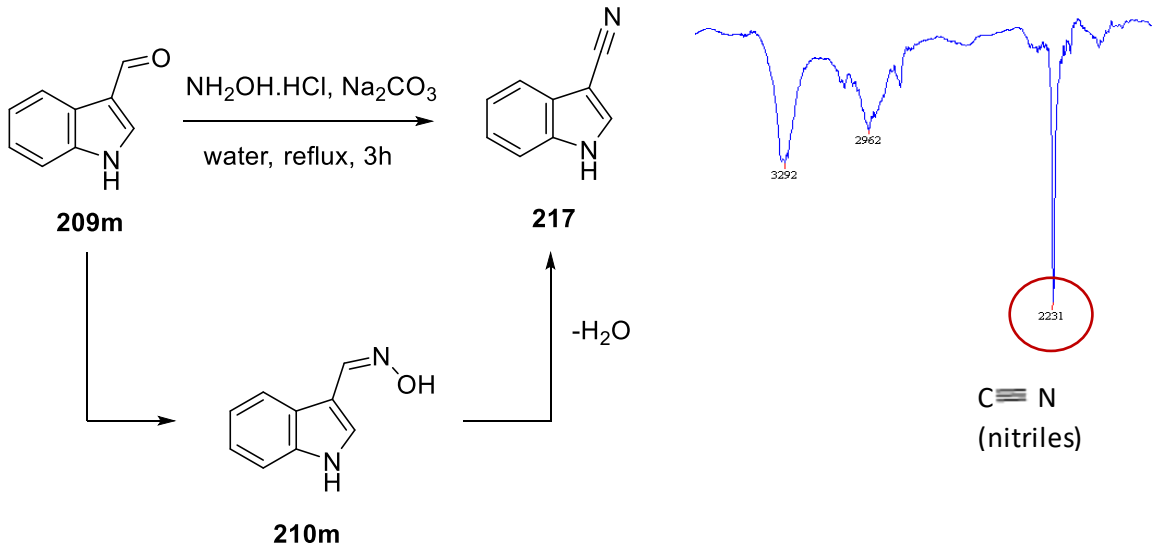


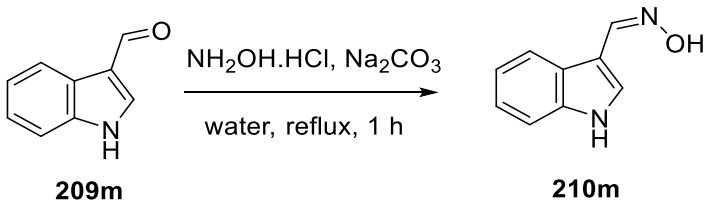
Figure 2.7 Oximes and hydroximoyl chloride derivatives

An anomaly was observed, when 1*H*-indole-3-carbaldehyde oxime (**209m**) was attempted to synthesise from the corresponding aldehyde, it lead to the formation of 1*H*-indole-3-carbonitrile (**217**) instead of the aldoxime. It was confirmed through GC-MS and IR, with m/z 142 and a strong peak at 2230 cm^{-1} corresponding to the CN (nitrile) respectively.



Scheme 2.22 Unwanted dehydration of 1*H*- Indole-3-carbaldehyde oxime to indole-3-carbonitrile and its IR spectrum

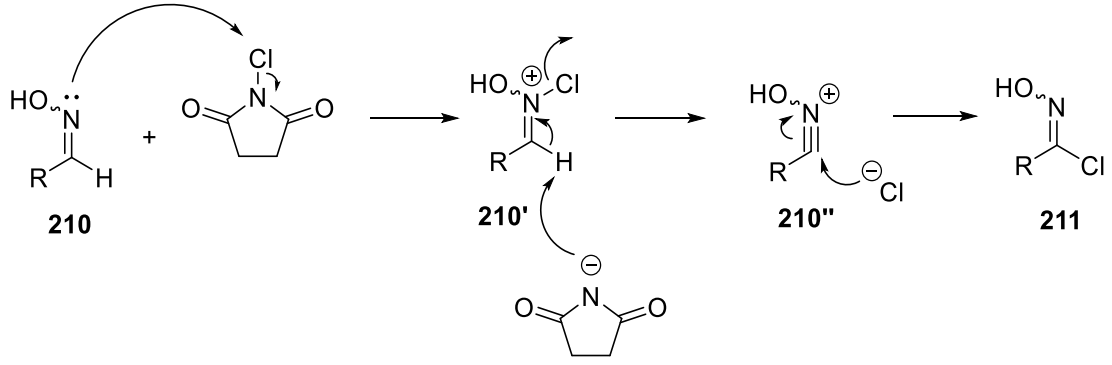
The conversion of aldehyde to nitrile through oxime is known in the literature,[86] wherein the oxime formed is dehydrated to nitrile in the presence of base. Similarly, here the formation of 1*H*-Indole-3-carbonitrile (**217**) would suggest that the 1*H*-indole-3-carbaldehyde oxime (**210m**) formed as an intermediate further undergoes dehydration. Expectedly, on reducing the reaction time to 1h resulted in the desired oxime product in excellent yields (Scheme 2.23). IR analysis showed the absence of the nitrile peak at 2230 cm^{-1}, with a new band at 1639 cm^{-1} (C=N stretching) confirming the product as 1*H*-indole-3-carbaldehyde oxime (**210m**). It was further confirmed by NMR and mass. A repeat experiment was also performed by putting the oxime back into the reaction, which gave nitrile (**217**) as the main product.



209m **210m**

Scheme 2.23 Synthesis of 1*H*-Indole-3-carbaldeyhyde oxime from 1*H*-Indole-3-carbaldehyde

The synthesis of hydroximoyl chlorides were carried out according to literature using *N*-chlorosuccinimide (NCS) as the chlorinating agent in *N*, *N*-dimethylformamide (DMF) as the solvent. In this method, NCS was slowly added (in portions) to a solution of aldoximes in DMF at ambient temperature. The initiation of the reaction was marked by a sudden increase in temperature (after 5-10 minutes of addition of first portion of NCS), sometimes external heat being necessary to initiate the reaction. The subsequent portions of NCS were added while maintaining the warm conditions (water bath was used, in case the temperature got too high). The cessation of heat indicated the completion of reaction, and the reaction was allowed to stir for 1 hour at room temperature. Once finished, the reaction mixture was poured into cold water, and extracted with DCM.



210 **210'** **210"** **211**

Scheme 2.24 Plausible mechanism for formation of chloroximes (**211**) from oximes (**210**)

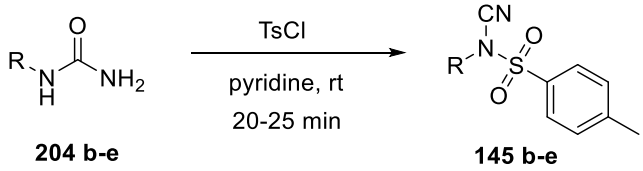
The organic fractions were evaporated and the residue purified by silica gel column chromatography to give hydroximoyl chlorides (**211a-k**). The mechanism of the NCS-chlorination of oximes is depicted in the Scheme 2.24.

Although the NCS-DMF chlorination worked in most of the substrates (Figure 2.7), it failed to provide the hydroximoyl chlorides in some cases. The *N*-hydroxyfuran-3-carbimidoyl chloride (**211-l**) was not obtained as black-lumpy precipitates were obtained which could be a result of the furan undergoing polymerisation Although the *N*-indolyl-carbimidoyl chloride (**211m**) has been reported in the literature, the NCS chlorination did not lead to the desired product. It can be speculated that ring chlorination could be a reason,[87] as has been observed with some activated (electron-rich) aldoximes.

2.3.2 Synthesis of *N*-aryl *N*-tosyl Cyanamides

Till 1949, *N*-aryl-*N*-tosyl cyanamides (**145**) were prepared by the action of toxic cyanogen bromide on arylsulfonanilides in the presence of sodium ethoxide. In 1949, Kurzer published his studies on the reaction of *N*-aryl ureas **204** with *p*-toluenesulfonyl chloride in pyridine, which gave **145** readily and in good yields. This method was advantageous as it avoided the use of toxic cyanogen bromide and is obtained in a time-efficient manner. The reaction uses an excess of the sulfonyl (tosyl) chloride, which acts as a dehydrating agent and facilitates the cyanamide formation (mechanism discussed in Ch-1, Scheme 1.21).

Table 2.6 Synthesis of *N*-substituted tosyl cyanamide derivatives



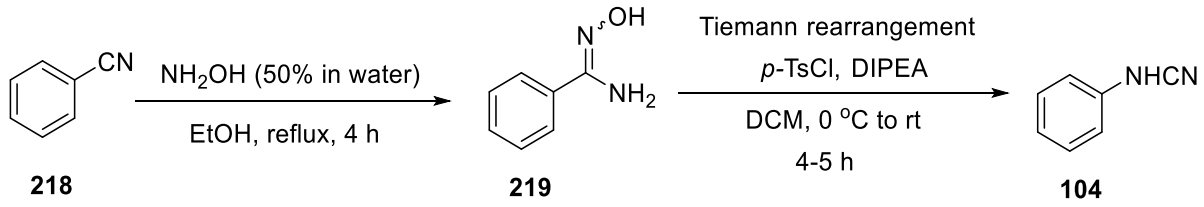
204 b-e → **145 b-e**

145b	**145c**	**145d**	**145e**
52%	32%	72%	0 %

Different cyanamide substrates bearing electron-withdrawing, electron-donating and alkyl groups were synthesised following the known procedure from the corresponding urea (Table 2.6).

The *p*-methoxybenzene *N*-tosyl cyanamide (**145b**) was synthesised in good yields, whereas the *p*-fluorobenzene *N*-tosyl cyanamide (**145c**) was obtained in a moderate yield of 32%. It has been reported by Kurzer that the reactions with halogenoureas are prone to polymerisation, where melamine-type compounds are formed as by-products along with the tosyl cyanamides resulting in low yields of the cyanamide.[88] While the *N*-methyl urea gave the corresponding cyanamide **145d** in good yields, *p*-nitrophenyl urea (**204e**) failed to return any product at room temperature. The reaction was further heated to reflux for 24 hours, which just returned the starting material. The reactions were monitored by TLC and IR, wherein no peak was observed at 2230 cm^{-1} (characteristic for NCN of the cyanamide).

Phenyl cyanamide (**104**) was prepared by facilitating Tiemann rearrangement of amidoximes[89] (**219**) using *p*-toluenesulfonyl chloride and DIPEA (Ch-1, section **1.7.2.1**). The corresponding amidoxime was synthesised from benzonitrile (**218**) by refluxing it with hydroxylamine in ethanol (Scheme 2.25).

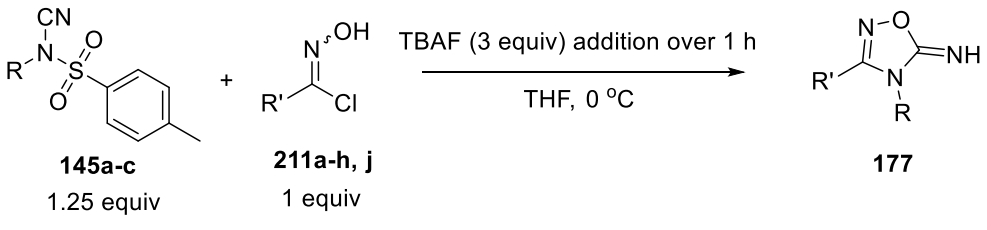


Scheme 2.25 Synthesis of phenyl cyanamide from benzonitrile by Tiemann rearrangement of amidoximes with *p*-toluenesulfonyl chloride

2.3.3 Investigating the substrate scope for the reaction

Having optimised the reaction conditions for benzonitrile oxide (**212**) generated *in situ* from phenyl hydroximoyl chloride **211a** in satisfactory yields, we decided to investigate other electron-rich and electron-poor nitrile oxides. Sterically hindered nitrile oxides are known to be relatively stable in solution,[90] hence a substrate like 2,4-dimethylbenzenehydroximoyl chloride (**211h**) was evaluated to gain an insight on the influence exerted by sterically hindered groups on the reaction. Heterocyclic substrates were also investigated to extend the scope the reaction. The results are represented in Table 2.7.

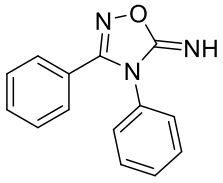
Table 2.7 Substrate scope of the cyanamide-nitrile oxide cycloaddition



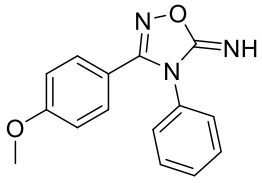
145a-c
1.25 equiv

211a-h, j
1 equiv

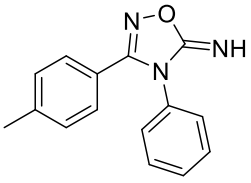
177



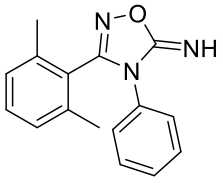
entry 1
214
79%



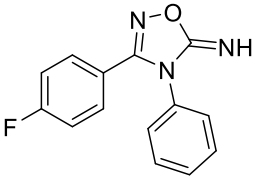
2
219
84%



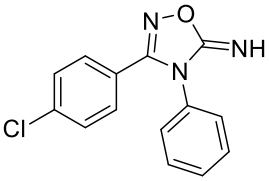
3
220
75%



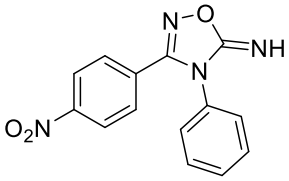
4
221
73%



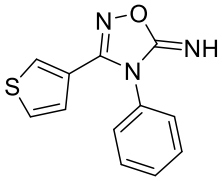
entry 5
222
63%



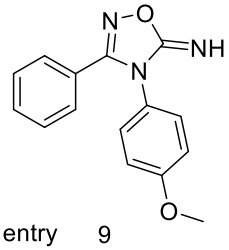
6
223
67%



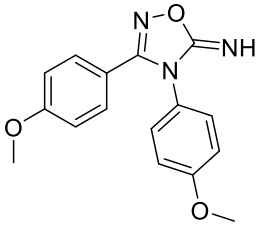
7
224
35% (53%)[a]



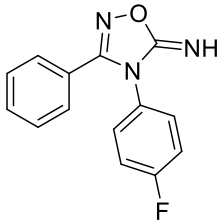
8
225
54%



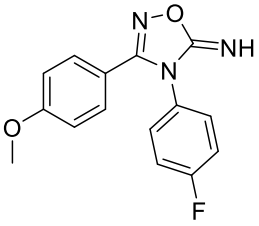
entry 9
226
68%



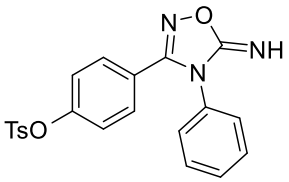
10
227
62%



11
228
89%



12
229
96%



entry 13
230[b]
42%

[a] one-shot addition of TBAF gave 53% yield, [b] *p*-hydroxyphenyl hydroximoyl chloride gave corresponding tosylated oxadiazol-5-imine product **230**

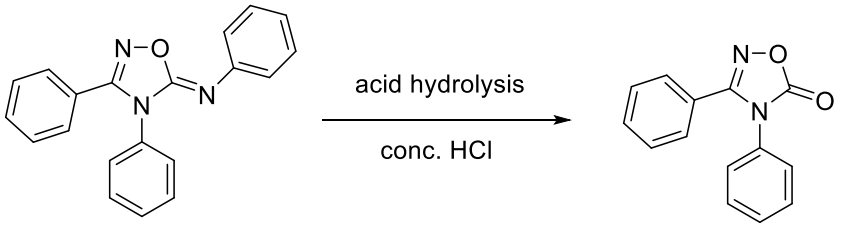
Both electron-rich (**211b-d**) and electron-poor (**211e-g**) nitrile oxide precursors participated in the reaction to render the cycloadducts (entry 1-3, 5-7, Table 2.7). The electron rich nitrile oxide precursor 4-methoxyphenylhdroximoyl chloride (**211d**) delivered the oxadiazol-5-imine (**219**) in 84 % yield. The 4-hydroxyphenylhydroximoyl chloride (**211c**) when reacted with TBAF under the optimised conditions gave the tosylated oxadiazolimine product **230** in 42% yield (entry 13, Table 2.7). The formation of tosylated product could be either due to the nucleophilic attack of the OH of hydroximoyl chloride on either NCTS or *p*-toluenesulfonyl fluoride (**205**). The sterically hindered nitrile oxide returned the desired product in good yields (73%, entry 4, Table 2.7), its stability in solution not yielding any advantage over benzonitrileoxide (79%)

Electronically poor substrates like *p*-chloro and *p*-fluoro phenylhydroximoyl chlorides **211e-f** gave moderate yields of the target oxadiazolimine (entry 5-6, Table 2.7). The *p*-nitrophenylhydroximoyl chloride (**211g**) gave poor yields of **224** (35%), due to the strong electron-withdrawing nature of the nitro group. The result was not surprising as the highly electron deficient nitrile oxides are known to be stabilised quickly in solution, making them less reactive.[91] Although, changing the rate of addition of TBAF (added in a single shot) returned an improved yield (53%) of the oxadiazolimine **224**. The cycloaddition protocol was also tolerated by heterocyclic substrate such as thiophenehydroximoyl chloride (**211j**) yielding the cycloaddition product **225** in 54 % yield (entry 8, Table 2.7)

Next, we decided to investigate the effect of the varying electronics on the *N*-aryl-*N*-tosyl cyanamide substrates. The reaction of phenylhydroximoyl chloride **211a** with *p*-methoxyphenyl tosyl cyanamide (**145b**) gave a good yield of 68%. However a union of electron-rich nitrile oxide with an electron rich cyanamide resulted in a decreased yield of 62% (entry 9 and 10, Table 2.7). A dramatic change in the reactivity pattern was observed with the introduction of the electron-deficient cyanamide substrate. 89 % yield was registered when the electron deficient *p*-fluorophenyl cyanamide (**145c**) was reacted with phenyl nitrile oxide precursor (**211a**) under optimised condition. Further, a combination of electron poor cyanamide with electron rich nitrile oxide offered the product (**229**) in an impressive 96 % isolated yield (entry 12, Table 2.7).

2.4 Synthesis of 1,2,4-oxadiazol-5(4*H*)-one

The 1,2,4-oxadiazolimine core could be functionalised further by hydrolysis to the medicinally important 1,2,4-oxadiazolone. The importance of the 1,2,4-oxadiazolone core in medicinal chemistry and as a synthetic intermediate has been discussed before (section **2.1**, Ch-2). Earlier reports by Huisgen on nitrile oxide cycloaddition[42] involved the synthesis of 1,2,4-oxadiazol-5-anil and its acid-catalysed hydrolysis to 1,2,4-oxadiazolone (Scheme 2.26).



184 **216**

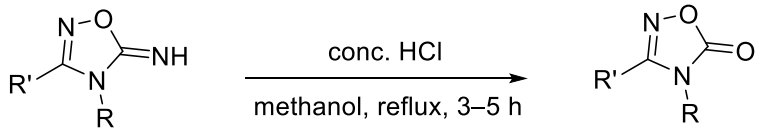
Scheme 2.26 Acid hydrolysis of the substituted imine to 1,2,4-oxadiazolone

We decided to use a similar approach for the hydrolysis of our substrate 1,2,4-oxadiazol-imine. Thus treating **214** with conc. HCl in methanol and refluxing the reaction mixture for 3 hours gave the 1,2,4-oxadiazolone (**216**) in excellent yield (95%, entry 1, Table 2.8). The reaction was observed to be slow at room temperature, hence reflux conditions were used. The procedure was tolerant to a number of differently substituted imine analogues including electron-rich, electron-deficient and heterocyclic substituents, furnishing the 1,2,4-oxadiazolones in excellent yields in 3-5 hours (85-95%, **231-235**, Table 2.8). The 1,2,4-oxadiazolones were characterised by the strong peak at 1770 cm^{-1} arising from the C=O (carbonyl stretch), along with comparison of NMR with the reference compounds.

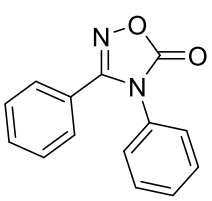
This method provides an easier and alternative route towards 1,2,4-oxadiazolones, which otherwise involves tedious, unreliable and multi-step protocols.[19-23]

1,2,4-oxadiazolones have been used as protecting groups and precursors to amidines,[14] as they are stable to acid and base under non-aqueous conditions, and easily removable under mild conditions. The highly basic nature of amidine makes it susceptible to hydrolysis to amides, which makes it difficult to work with amidines without the defense of a protecting group. So, the next logical step was to use the 1,2,4-oxadiazolone compounds obtained by hydrolysis of 1,2,4-oxadiazol-imine to access amidines. Amidine groups are found in many medicinal drugs as well as are important intermediates in chemical transformations (as described in section **2.1**, Ch-2).

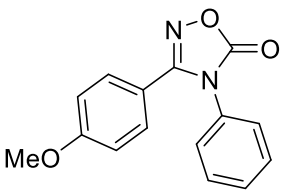
Table 2.8 Hydrolysis of 1,2,4 oxadiazol-5 (4*H*)-imines to 1,2,4 oxadiazol-5(4*H*)-one



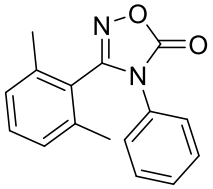
214, 219, 221-223 **216, 231-235**



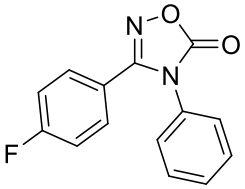
entry 1
216
95 %



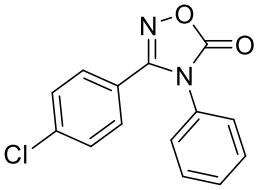
2
231
86 %



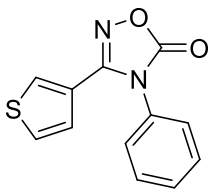
3
232
91 %



entry 4
233
95 %

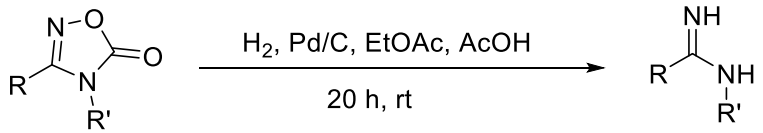


5
234
91 %

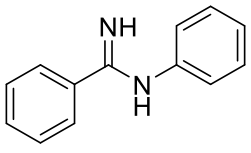


6
235
89 %

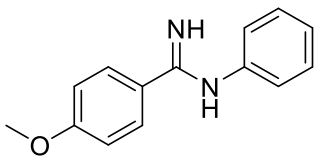
Table 2.8 Pd/C catalysed reduction of 1,2,4-oxadiazol-5(4*H*)-one to amidines



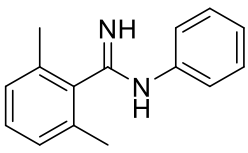
216, **231-232** **236-238**



entry 1
236
94%



2
237
91%



3
238
89%

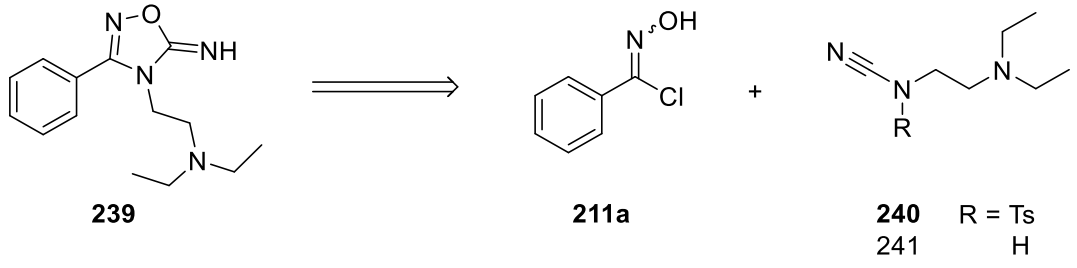
Among the methods known in literature for the synthesis of amidine from oxadiazolones include the catalytic reduction using Pd/C with H_2[14a] or Zn/HOAc.[92] The reductive decarboxylation with these catalytic systems involves the reduction of the N-O bond which releases the amidine. The hydrogenation of an ethyl acetate solution of the oxadiazolone **216** in presence of 10% Palladium on carbon (Pd/C) and 1 molar equivalent of acetic acid was attempted, which furnished the amidine **236** in an excellent yield of 94%. Similarly, the *p*-methoxy and 2,4-dimethoxy amidine derivatives (**237-238**) were obtained in excellent yields without the need of any tedious purification step (entry 2-3, Table 2.8).

2.5 Aliphatic substrates and imolamine

Studies were conducted to extend the established cyclisation protocol to include the aliphatic substrates to demonstrate access to drug molecules like Imolamine (**239**, Figure 2.1, Ch-2). The drug Imolamine, an 1,2,4-oxadiazol-5(4*H*)-imine derivative is a known coronary vasodilator,[93] which has been tested for acute and chronic coronary insufficiency[94] as well as for the long-term treatment of angina pectoris.[95] However, mot much studies have been carried out since the late 1970s.

As previously discussed, a stepwise route which included a 1,3-dipolar cycloaddition of cyanamide with nitrile oxide to the 1,2,4- oxadiazole-5-amine, followed by isomerisation and an alkylation has been reported in 1960's by Steren (Scheme 2.6).

We decided to use our optimised one-pot method to synthesise Imolamine, which could be beneficial than the step-intensive method reported in the literature. Retrosynthetically, the union of the *N*-alkyl cyanamide **240** with the nitrile oxide precursor **211a** would give imolamine (Scheme 2.27).

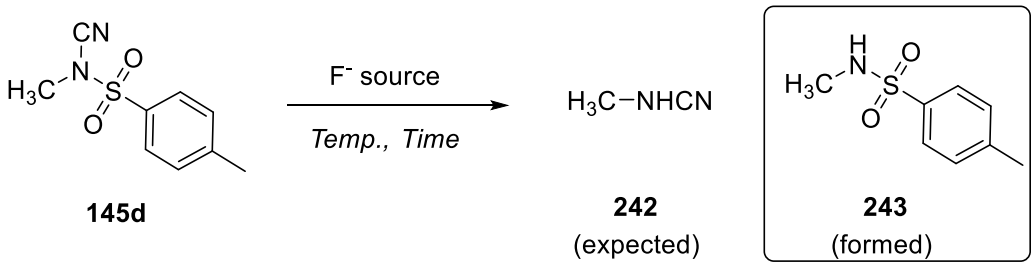


Scheme 2.27 Proposed retrosynthesis of the drug imolamine (**239**)

The synthesis of the (*N*,*N*-diethyl) ethyl cyanamide **240** was thought to be the bottle-neck in the synthesis of the imolamine as the compound was not known in the literature. We decided

to start with a simple *N*-alkyl cyanamide like *N*-methyl-*N*-tosyl cyanamide (**145d**) and check its detosylation for the generation of the cyanamide ion and consequently its reaction with nitrile oxide. Various fluoride sources like ammonium fluoride (NH_4F), potassium fluoride (KF), CsF and TBAF were screened for the detosylation of **145d** (Table 2.10).

Table 2.10 Screening of fluoride source for the detosylation of *N*-methyl-*N*-tosyl cyanamide



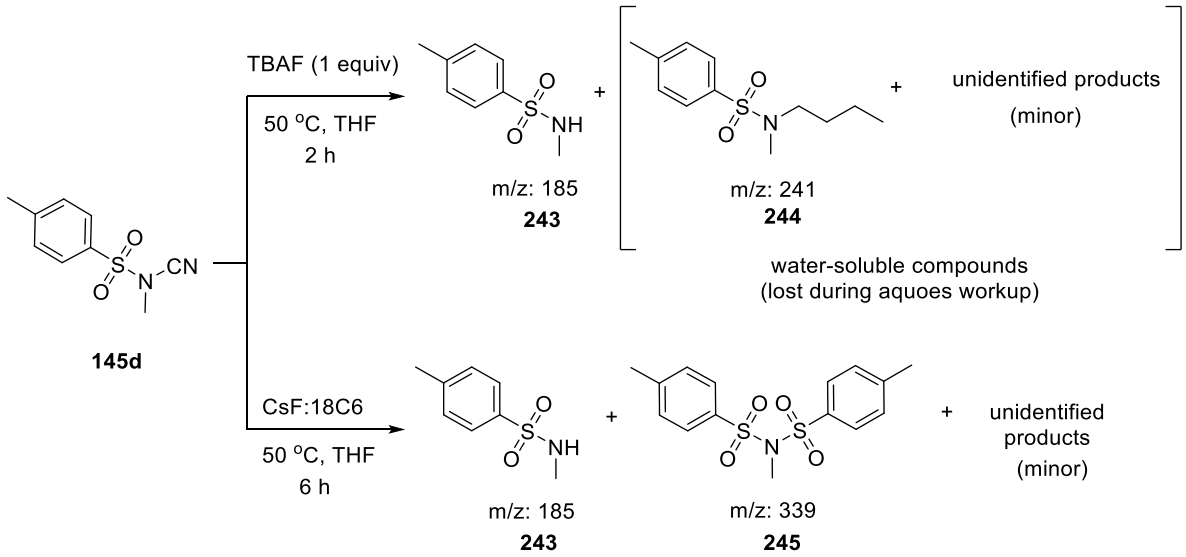
145d **242** (expected) **243** (formed)

Entry	F^- Source	Mol Equiv.	Temp (°C)	Time (h)	% Conversion[c]
1	NH_4F	6[a]	rt	24	0 %[d]
2	KF	6[a]	rt	24	trace [d]
3	TBAF	3[b]	rt	Overnight	100%
4	TBAF	1	50	2	100%
5	CsF	4[b]	rt	Overnight	40%
6	CsF:18-C-6	3:4	rt	Overnight	60%
7	CsF:18-C-6	3:4	50	6	70 %
8	CsF:18-C-6	6:4	rt	12	100%

[a] first screened with 1, 2 and 4 molar equivalents, TLC analysis showed no new spots, [b] screened with 1 and 2 molar equivalents with major spots for starting material on TLC, [c] monitored by GC-MS, % conversion calculated using peak area, [d] monitored by TLC

Reactions with NH_4F (6 mol equiv.) and KF (6 mol equiv.) in THF at room temperature were monitored by TLC, which showed no major spots except the starting material **145d** (entry 1 and 2, Table 2.10). The more nucleophilic TBAF (3 mol equiv.) resulted in the complete consumption of the starting material when kept overnight at room temperature (entry 3, Table 2.10). However, the reaction time was reduced to 2 hours when the reaction mixture was heated to 50 °C (entry 4, Table 2.10). Similarly after trying different molar equivalents of CsF and its combination with 18-crown-6, 100% consumption of the starting material was achieved with 6:4 molar ratio of CsF: 18-crown-6 in 12 hours at room temperature (entry 5-8, Table 2.10, analysed by TLC and GC-MS).

Surprisingly, the GC-MS analysis of the reaction mixtures indicated that the main product in the above reactions was *N*-Methyl-*p*-toluenesulfonamide (**243**, decyanation product), instead of the expected *N*-methyl cyanamide (**242**, detosylation product). The decyanation of **145d** was found to be favoured over the detosylation as no detosylated product nor the signature *p*-toluenesulfonyl fluoride (**205**, *m/z* = 174) could be detected on the GC-MS spectrum.



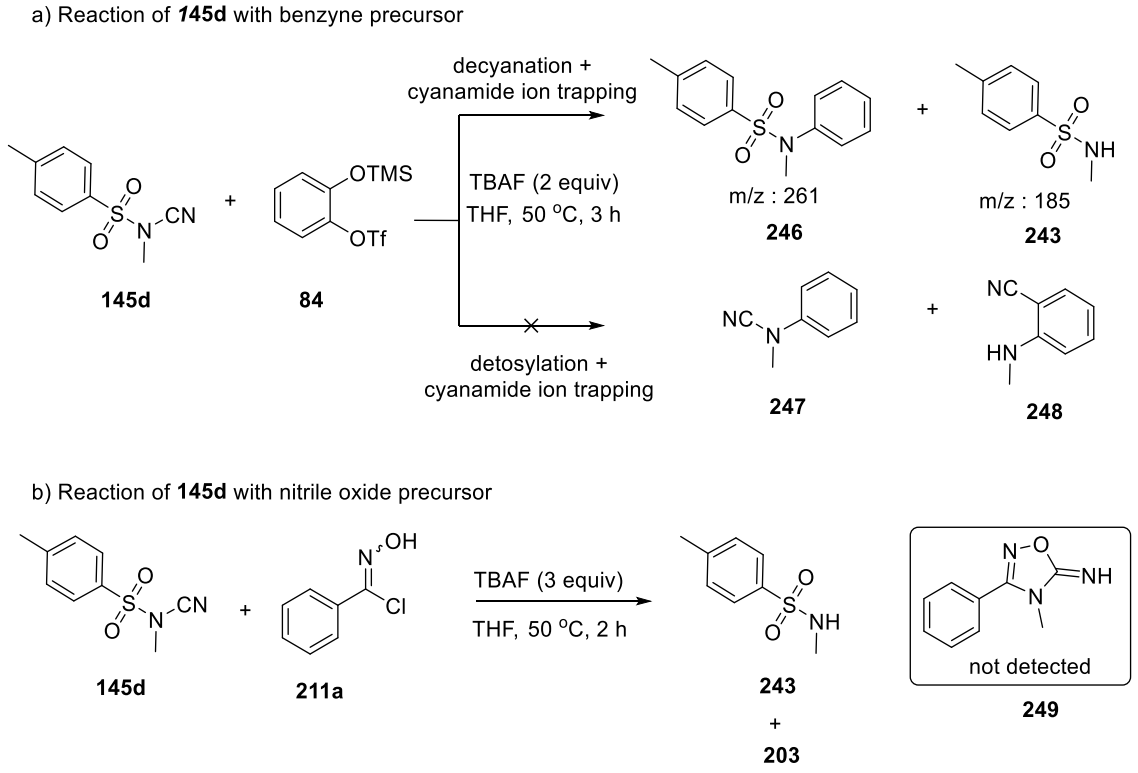
Scheme 2.28 Products formed by the reaction of *N*-methyl-*N*-tosyl cyanamide (**145d**) with fluoride sources

The reaction of **145d** with TBAF at 50 °C gave a major peak corresponding to the decyanated product **243** (*m/z* 185), along with some water-soluble by-products which were not visible on the GC-MS spectrum after workup (Scheme 2.28). The decyanated product was also the main product in the CsF:18-crown-6 reaction along with some minor by-products (GC-MS). The reaction also gave **245** as a product on heating (not observed at room temperature), which may

have formed by the nucleophilic attack of the decyanated product **243** on the parent cyanamide **145d** (Scheme 2.28).

In order to further confirm the unprecedented fluoride-assisted decyanation, it was decided to react the methyl cyanamide **145d** with 2-(Trimethylsilyl)phenyl Trifluoromethanesulfonate- a benzyne precursor (**84**) (Scheme 2.29). The reaction proceeded through the decyanation route giving the sulphonamide product **246**, which was a major peak in the GC-MS spectrum with *m/z* 261 along with the decyanated product **243**. The reaction of the methyl cyanamide with the target hydroximoyl chloride (**211a**) failed to yield any desired oxadiazolimine (**249**) product (Scheme 2.29). Instead the diphenyl furoxan (**203**) and decyanated product **242** were detected as the major peaks in the GC-MS spectrum.

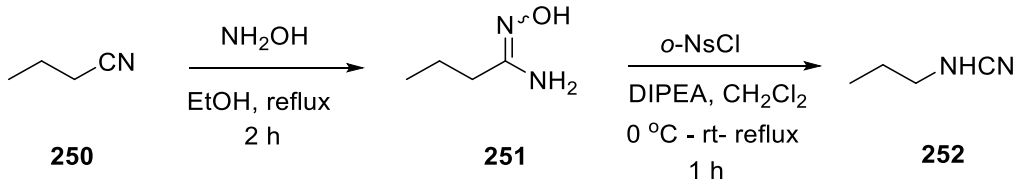
Thus, the utilisation of different fluoride sources for the detosylation of *N*-methyl *N*-tosyl cyanamide (**145d**) resulted in decyanation instead of expected detosylation as seen in the aromatic counterparts. It should be noted that a fluoride-assisted decyanation and particularly in alkyl tosyl cyanamides is unprecedented, and could be a subject of future studies. Moreover, the generation of cyanuric fluoride could be investigated, which is a known fluoride source.



Scheme 2.29 Reactions of *N*-methyl-*N*-tosyl cyanamide (**145d**) with (a) benzyne precursor and (b) nitrile oxide precursor

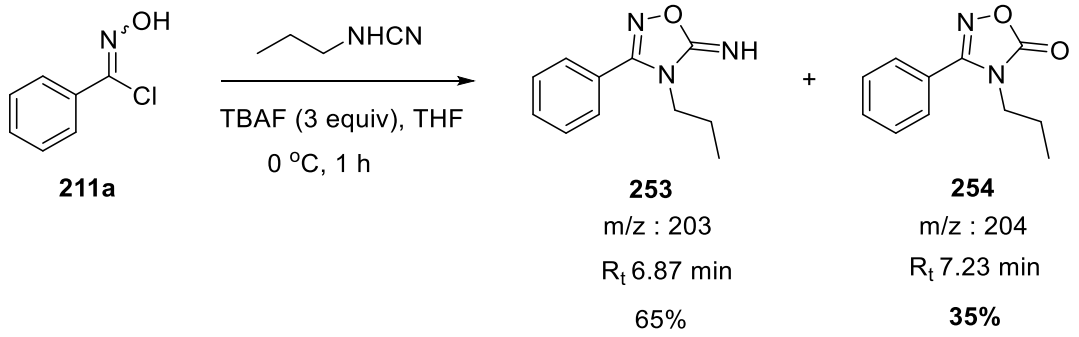
Cyanuric fluorides have wide applications including synthesis of acid fluorides from carboxylic acid, deoxygenation of alkyl sulfoxides, reduction of acids to alcohols and activation of alkenyl boronic acids for 1,4-addition reactions.

Next, we decided to use unsubstituted alkyl cyanamides, as phenyl cyanamide (**104**) is known to participate in the cyclisation reaction with nitrile oxides. Propyl cyanamide (**252**) was synthesised in two steps starting from butyronitrile (**250**) with the formation of amidoxime **251** as the intermediate step. The tiemann rearrangement of aliphatic amidoximes have been reported by Lin *et al.*[89] with *o*-nosyl chloride (*o*-NsCl) and DIPEA in dichloromethane (Scheme 2.30).



Scheme 2.30 Synthesis of propyl cyanamide by tiemann rearrangement of amidoxime

The propyl cyanamide was then treated with phenyl hydroximoyl chloride (**211a**) in presence of TBAF (3 mol equiv.) in THF according to the optimised method (Scheme 2.30). When the reaction mixture was analysed by GC-MS, gratifyingly it showed the formation of the desired oxadiazol-5-imine (**253**) along with the hydrolysed product- oxadiazolone (**254**) in a 65:35 ratio as calculated from the peak area of the GC-MS chromatogram (Figure 2.8).



Scheme 2.31 Reaction of propyl cyanamide with **211a** in presence of TBAF

It was suspected that the hydrolysis might have taken place during the aqueous mini-workup for the GC-MS sample preparation. Furthermore, during the scale-up, when the crude reaction mixture was loaded onto silica gel, further hydrolysis and degradation was observed as new spots could be seen forming on the TLC. This could be due to the acidic nature of the silica

gel. In order to prevent the hydrolysis and degradation, the reaction mixture was loaded onto a neutralised silica gel column without workup and the product **253** was isolated in 35% yield. The product was further confirmed by NMR, HRMS and IR (characteristic 1689 cm^{-1} band for exocyclic C=N) studies.

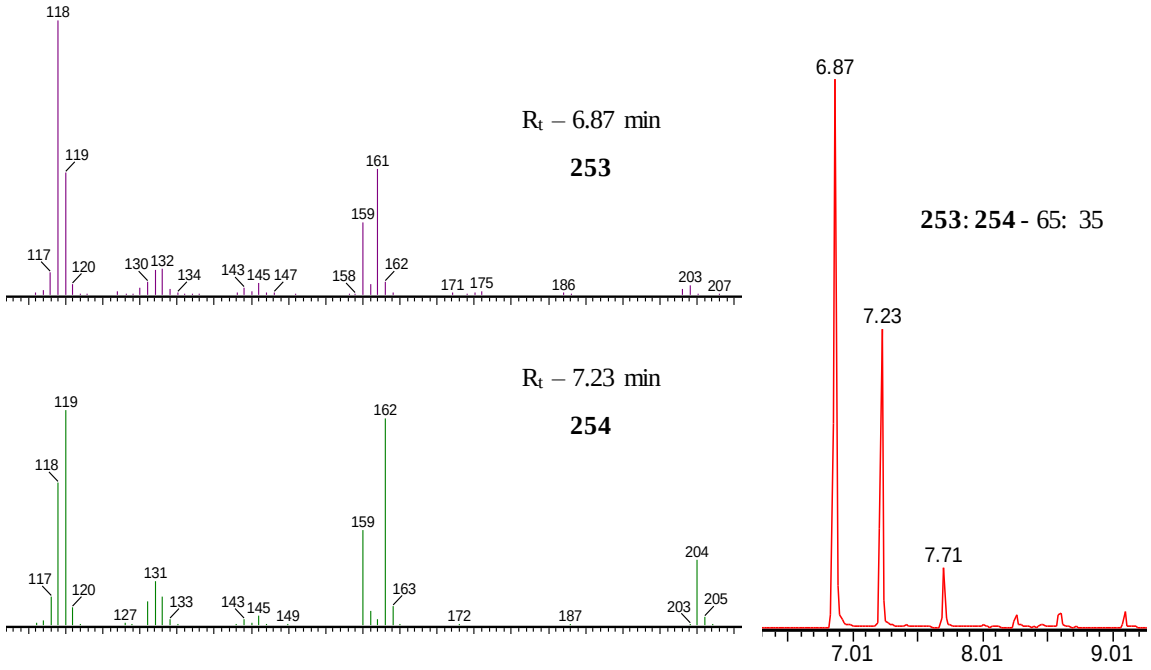
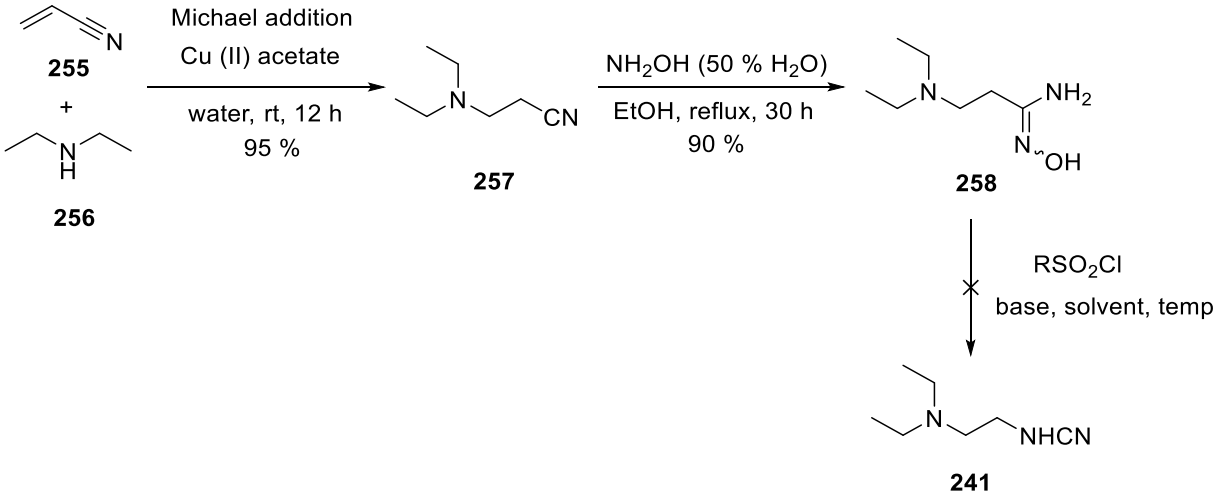


Figure 2.8 Part of the GC-MS chromatogram and spectrum for the reaction in scheme 2.30

2.6 Efforts towards the synthesis of 'Imolamine'

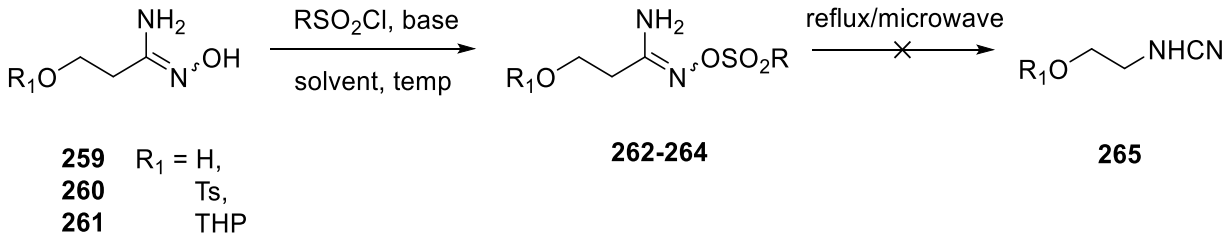
2.6.1 Tiemann rearrangement of amidoximes

The key step for imolamine synthesis was the synthesis of the corresponding alkyl cyanamide **241**. Synthesis of aliphatic cyanamides has been accomplished using tiemann rearrangement of amidoximes[89] (Scheme 2.30), hence a similar approach was envisaged for the synthesis of alkyl cyanamide **241**. The corresponding amidoxime **258** was synthesised starting from acrylonitrile (**255**) and diethyl amine (**256**) in a two-step reaction sequence (Scheme 2.32).



Scheme 2.32 Attempted synthesis of **241** by Tiemann rearrangement

Subjecting the amidoxime **258** to conditions reported by Lin *et al.* did not yield the cyanamide **241** as expected. A variety of benzenesulfonyl chlorides, base, solvents and temperature were screened for the reaction, with no positive results. Next, the rearrangement was attempted with 2-hydroxyethylamidoxime (**259**) in presence of *p*-TsCl and DIPEA in DCM at room temperature,[89] but *O*-tosylamidoxime (**262**) was isolated as the sole product (Scheme 2.33).

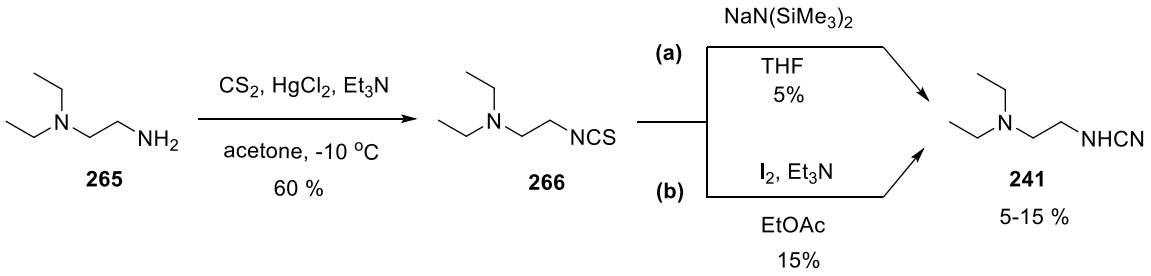


Scheme 2.33 Attempted synthesis of **265**

Lin and colleagues proposed that the heterolytic N-O bond cleavage of the amidoxime was the driving force for the rearrangement. Hence, *o*-nitrobenzenesulfonyl chloride (*o*-NsCl) was employed instead of *p*-TsCl to provide a better leaving group, and the reactions carried out at higher temperatures. The reaction was also carried out using different base (pyridine, DMAP) and under microwave heating conditions (70-140 ^{o}C), but the rearrangement of **262** was not observed. Tosyl and THP protected hydroxyethyl amidoxime (**260-261**) also returned the sulfonylated product (**263-264**). With the failure to synthesise the cyanamide (**241** and **265**) by amidoxime rearrangement, other approaches were tried.

2.6.2 Desulfurisation of thioureas and isothiocyanates

Desulfurisation of thioureas and isothiocyanates provide another route towards cyanamide synthesis (section **1.7.2.1**, Ch-1). The *N*,*N*-diethylaminoethyl isothiocyanate (**266**) was prepared from the corresponding amine (**265**) using a previously reported procedure from McElhinney,[96] using carbon disulphide (CS_2) and $HgCl_2$ in acetone. Removal of the mercury salts by filtration, followed by chromatographic purification, provided the isothiocyanate **266** in 60% yield. Direct desulfurisation of the isothiocyanate using a hindered base like $NaN(SiMe_3)_2$, yielded the cyanamide **241** in poor yield (5%, Scheme 2.34a). Next, desulfurisation of thioureas formed by the action of ammonia on **266** was attempted using iodine as the desulfurizing agent to give the corresponding cyanamide **241** in inferior yields (15%, Scheme 2.34b). The difficulties in the isolation of the pure product as well as the unstable nature of **241** were found to be the reasons for poor yield. No further synthesis was carried out in pursuit of the cyanamide **241**.



Scheme 2.34 Synthesis of target cyanamide **241** by desulfurisation of isothiocyanates and thioureas

The traditional synthesis route of cyanamide involving cyanation of the corresponding amine **265** was not attempted owing to the known toxicity of cyanogen bromide (CNBr) gas. Hence, most of the efforts were put into alternative methods of cyanamide synthesis.

2.7 Mechanistic studies

Computational studies were performed by colleagues at University of Nottingham to determine the reaction mechanism and understand the nature of the bonding within the cyanamide ion (**189**). Density functional theory calculations were employed using the ωB97X functional[97] 6-31+G* (geometries)[98] and 6-311++G** (energies)[99] basis sets. The cyanamide ion was found to retain the triple bond to the terminal nitrogen (−CN2), while fitting partial atomic charges to the electrostatic potential revealed that the negative charge was localised on N1 (Figure 2.9).

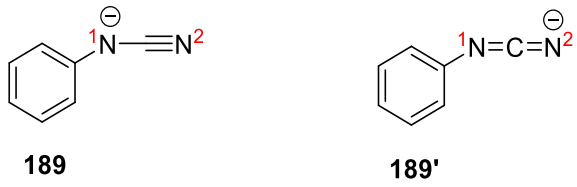
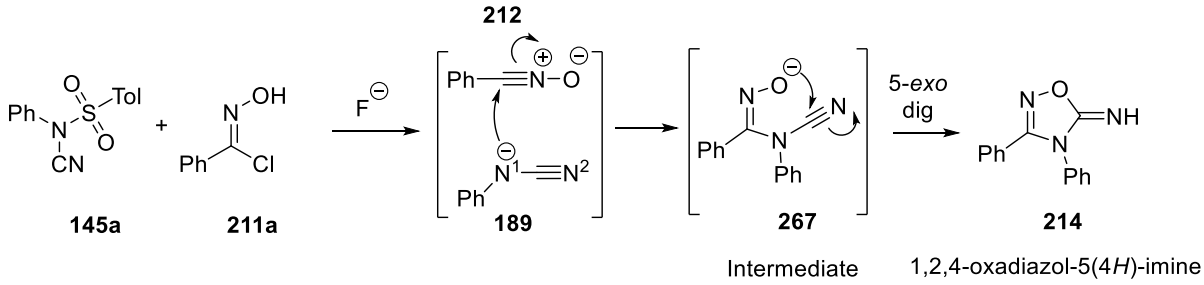


Figure 2.9 Phenyl cyanamide and carbodiimide structures

The reaction was found to proceed via the stepwise cyclisation pathway, while no transition state could be located for the concerted mechanism (Scheme 2.35). The reaction profile is shown in Figure 2.9, the stationary points being the two transition states and the intermediate **267**. The presence of the intermediate structure **267** signifies the initial attack of the cyanamide ion on the electrophilic centre of the nitrile oxide, which then undergoes a ring closure in an *exo*-dig fashion. The reaction shows a low barrier for the cyclisation step of the intermediate (**267**) to the product (**214**).



Scheme 2.35 Reaction mechanism for the cyclisative capture of cyanamide ion with nitrile oxide

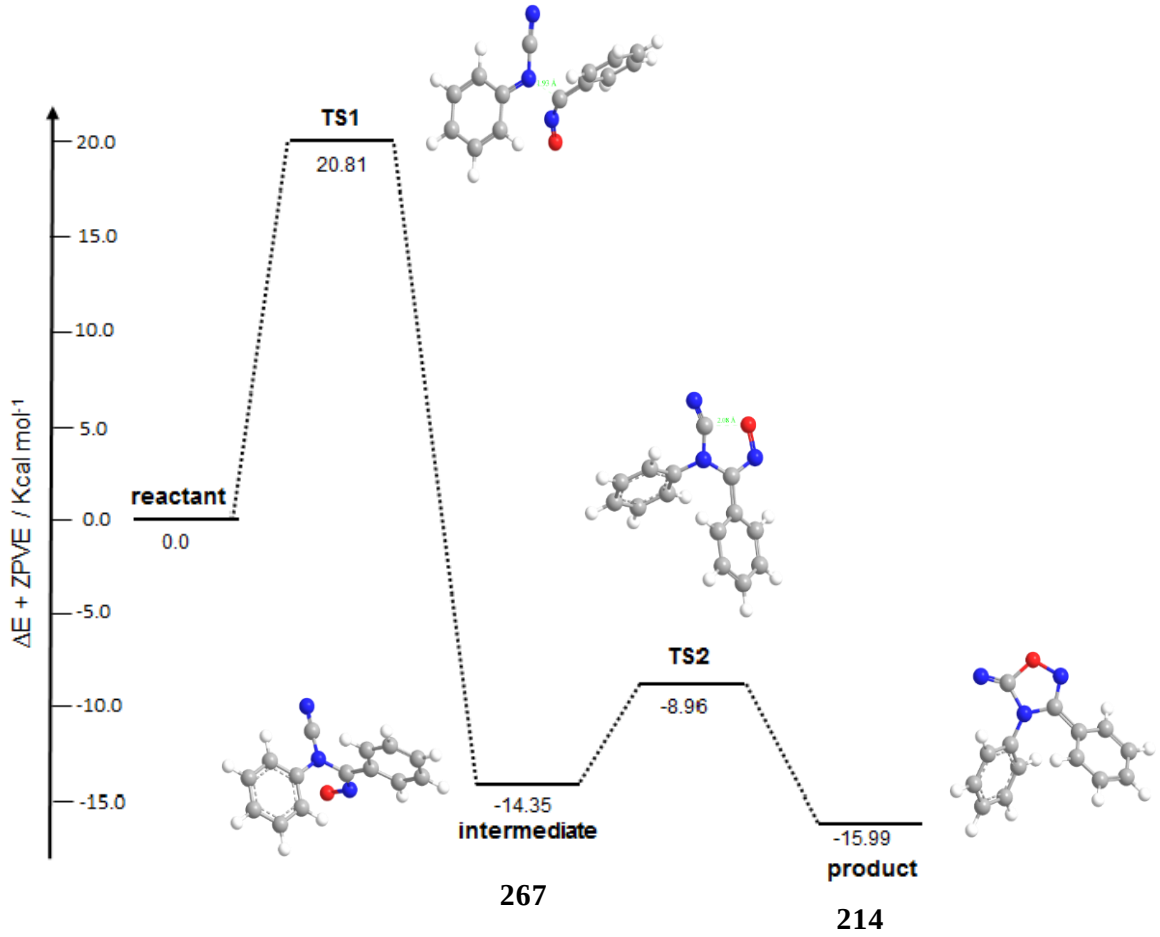


Figure 2.9 Reaction energy profile calculated using ωB97X/6-311++G(d,p)//ωB97X/6-31+G(d) in the gas phase.

2.8 Conclusions and future studies

In summary, the present protocol describes an expedient one-pot access to 1,2,4-oxadiazol-5(4*H*)-imines (**177**) in good to excellent yields from cyanamide ion and nitrile oxide generated *in situ*. The use of cyanamide as a three-atom two centre dipolarophile like species and its reaction with a 1,3-dipole (nitrile oxide) has been achieved, leading to a cyclisation product through a formal [3+2] cycloaddition route. The reagent toolkit further offers access to yet other pharmacologically and chemically significant cores such as oxadiazolones and amidines in a very straight forward manner.

As a part of future studies, the synthesis of imolamine can be carried out using the existing protocol. The synthesis of the corresponding cyanamide for the cyclisation with nitrile oxide has been attempted, but the low yields and instability problem persist. Efforts can be made

towards solving this problem, as it would further the scope for use of aliphatic cyanamides in heterocycle synthesis.

2.9 References

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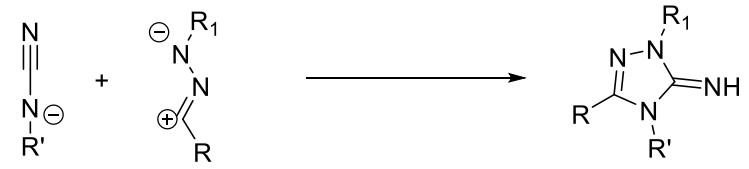
Chapter-3

Reaction of Cyanamide ion with Nitrile imine 1,3-dipole

Chapter 3

Reaction of Cyanamide ion with Nitrile imine 1,3-dipole

Our studies with NCTS established the generation of cyanamide ion and its *in situ* cyclisative capture with 1,3-dipole nitrile oxide to offer oxadiazol-5-imine as the product. Continuing with our studies on construction of new and under-represented heterocyclic cores, we were keen to extend the methodology to some other reactive 1,3-dipole *viz* nitrile imine.



199 268 180

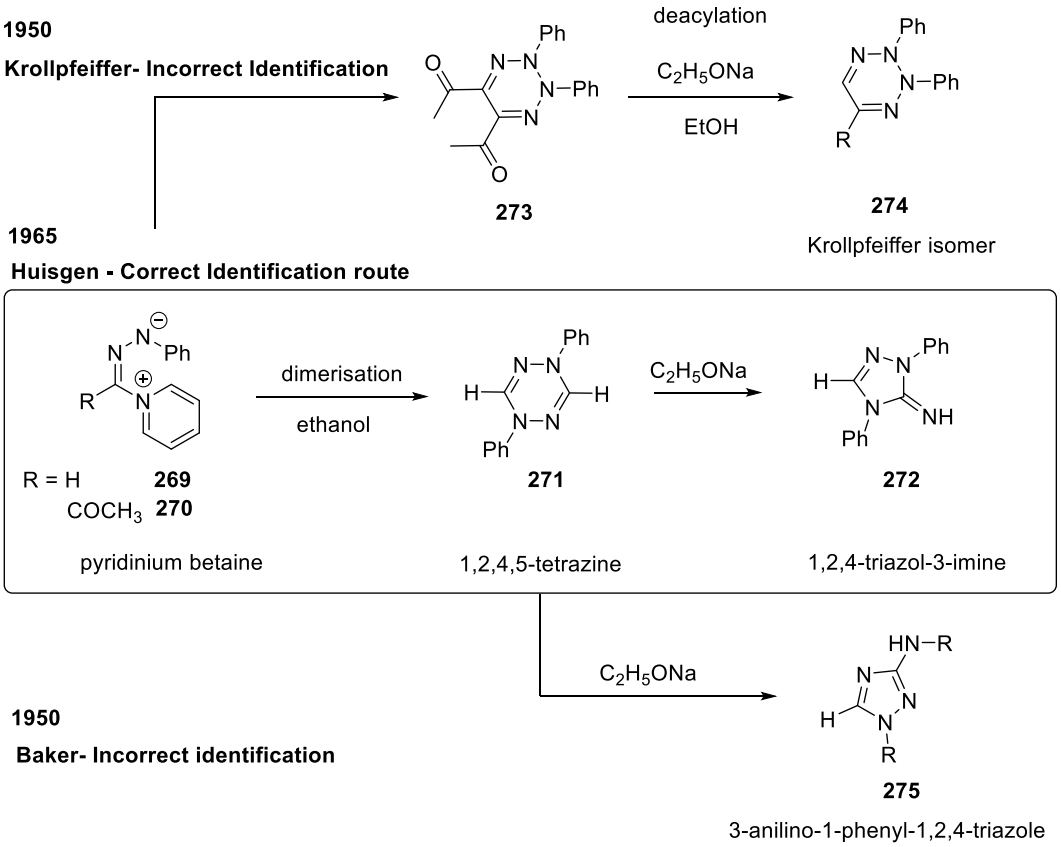
Scheme 3.1 Cyclisative capture of cyanamide ion by nitrile imine

The present work explores the synthesis of a heterocyclic imine – 1,2,4-triazole-3-imine (**180**) *via* the *in situ* reaction of cyanamide ion with nitrile imine, as illustrated in Scheme 3.1.

3.1 1,2,4-Triazol-3-imine

1,2,4-Triazol-3-imine (**272**) was first synthesised in 1950 by Krollpfeiffer *et al.*[1] and Baker *et al.*[2] independently, but erroneously identified as another product. Krollpfeiffer identified it as a deacylation product of **273**, a 1,2,3,4-tetrazine compound **274**, whereas Baker *et al.* identified the rearranged product of 1,2,4,5-tetrazine (**271**) as 3-anilino-1-phenyl-1,2,4-triazole (**275**, Scheme 3.2).

In 1965, Huisgen[3] corrected the dimerised product of pyridinium betaine **269** as 1,2,4,5-tetrazine (**271**), and the sodium ethoxide treated product as 1,2,4-triazol-3-imine (**272**) using detailed UV and IR studies (Scheme 3.2). He showed that an IR value of 3320 cm^{-1} for NH vibration and 2 C=N bands at 1632 cm^{-1} and 1565 cm^{-1} were incompatible with both **274** or **275**. Huisgen demonstrated that the sodium ethoxide (0.6%) driven rearrangement of 1,2,4,5-tetrazine (**271**) to 1,2,4-triazol-3-imine (**272**) was reversible and **271** could split into 2 molecules of phenyl cyanamide (**104**) on heating. On heating **271** with 10% sodium ethoxide in ethanol, phenyl cyanamide (**104**) was furnished in 66% yield (Scheme 3.3a).

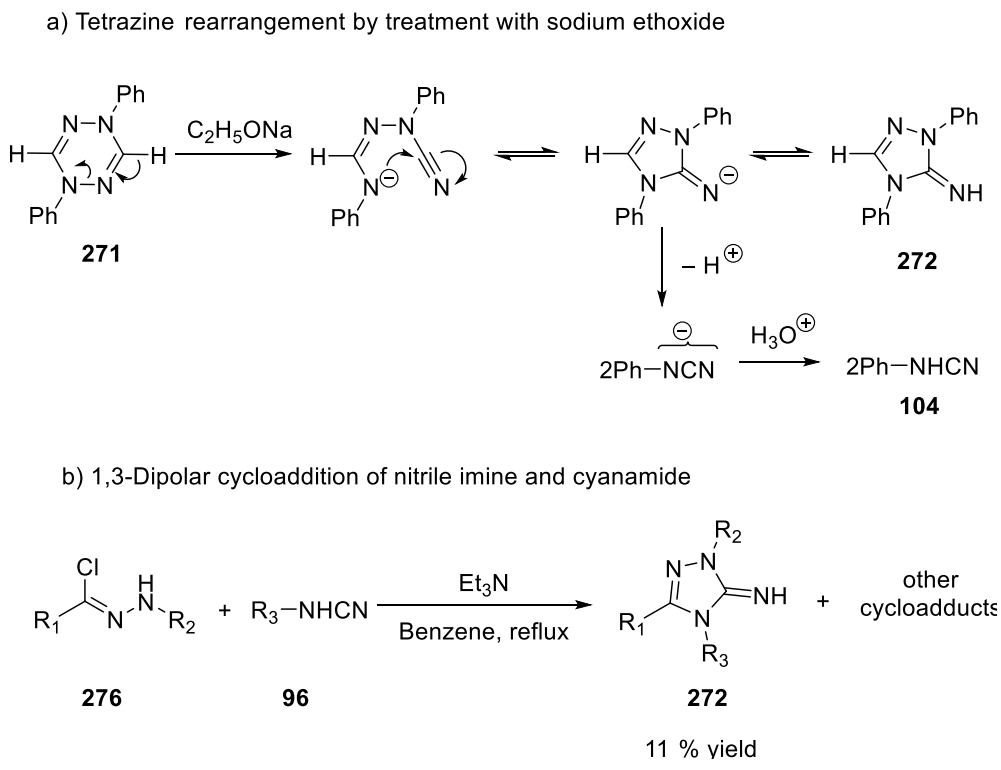


Scheme 3.2 Identification and first synthesis of 1,2,4-triazol-3-imine (**272**)

Further confirmation of the structure of **272** was given by Huisgen *via* synthesis, as a cycloaddition product of nitrile imine (**268**) and cyanamide (**96**), albeit in lower yields[4] (Scheme 3.3b). Huisgen proposed that the cycloaddition product could be due to the reaction of the carbodiimide tautomer of the cyanamide or through an open chain intermediate structure. The 1,2,4-triazol-3-imine (**180**) was isolated only in 11% yield, as the *exo*-cyclic C=NH of **180** acted as a dipolarophile to undergo further reactions with nitrile imine and yield other cycloadducts (Scheme 3.3b).

3.2 Nitrile imine as 1,3-dipole

Ever since its discovery by Huisgen,[5,6] nitrile imines have been vastly utilised in organic synthesis, predominantly in regioselective dipolar cycloaddition reactions leading to a variety of five-membered heterocycles like pyrazole, triazole, etc. (as illustrated in Scheme 1.9, Ch-1).[7] Recently they have garnered much interest amongst theoretical chemists debating the structure and reactivities of nitrile imines.[8,9]



Scheme3.3 Synthesis of **272** by - a) rearrangement of tetrazine, b) cycloaddition of nitrile imine and cyanamide

Huisgen classified nitrile imine 1,3-dipoles under two categories: allenic and propargylic type, which were described by their resonance structures attributed to the single-minimum potential energy wells (Figure 3.1). Nitrile imine, being a flexible system with four π electrons distributed over three atoms, it can be written in six different canonical forms which include: allenic, propargylic, carbonic, 1,3-dipolar, reverse 1,3-dipolar and 1,3-biradical. Recently, theoretical studies accompanied with matrix isolation and IR spectroscopy of the largely elusive nitrile imines have indicated mainly allenic (IR absorptions for C=N - 2000-2100 cm^{-1}) and propargylic (IR absorptions for nitrile – 2200 cm^{-1}) structures for nitrile imine.[9]

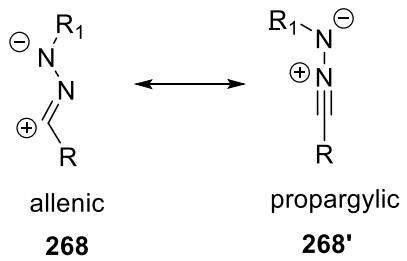
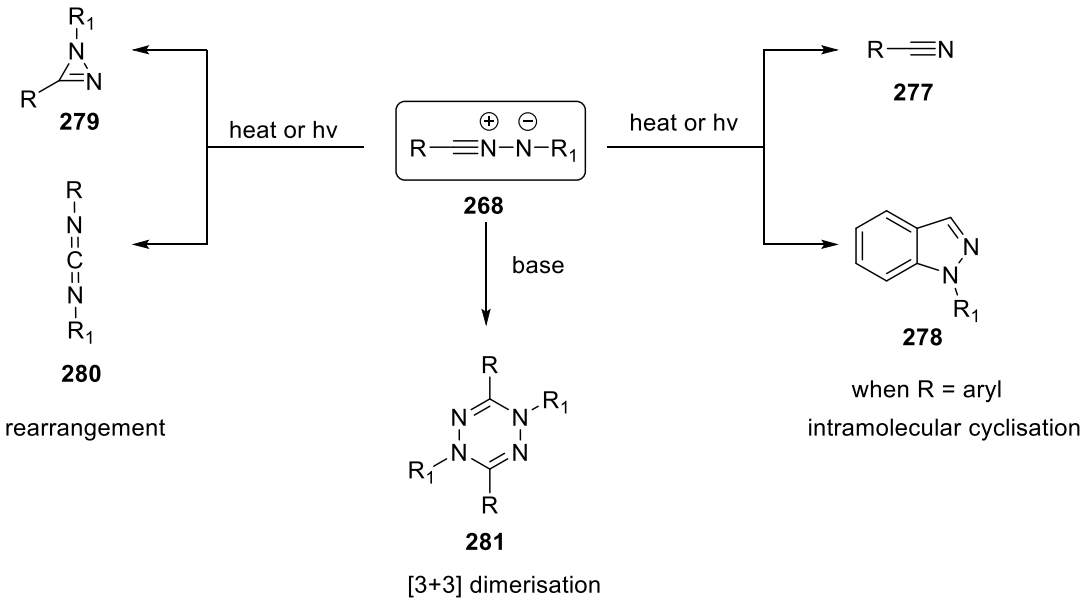


Figure 3.1 Resonance structures of nitrile imine: allenic and propargylic forms

Recently, Wentrup and colleagues discovered the existence of two different structures for nitrile imine (phenylnitrile imine) corresponding to two different energy minima, representing bond-shift isomers. The two isomers ─ allenic and propargylic nitrile imines were captured in a matrix and characterised by IR spectroscopy, suggesting the two forms are not resonance structures but bond shift isomers. This was the first observation of a 1,3-dipole existing in two different structures.[10]

With evidence for the existence of carbenic form of nitrile imine as well,[8] the understanding of the structures of nitrile imine has increased considerably over the past few years. However, the effect of these structures on the reactivities of nitrile imines have eluded researchers especially with substituted nitrile imines, as all forms of nitrile imines have been found to undergo different 1,3-dipolar cycloadditions without much distinction.[8]

Nitrile imines are known to be short-lived intermediates and readily undergo [3+3] cycloaddition in presence of base to a tetrazine[5] (**281**) (Scheme 3.4). They are also known to rearrange to azirines (**279**) or carbodiimides[11] (**280**) in the presence of a heat or UV source, fragment to nitriles[12] (**277**) or even undergo intramolecular cyclisation to indazoles[13] (**278**).

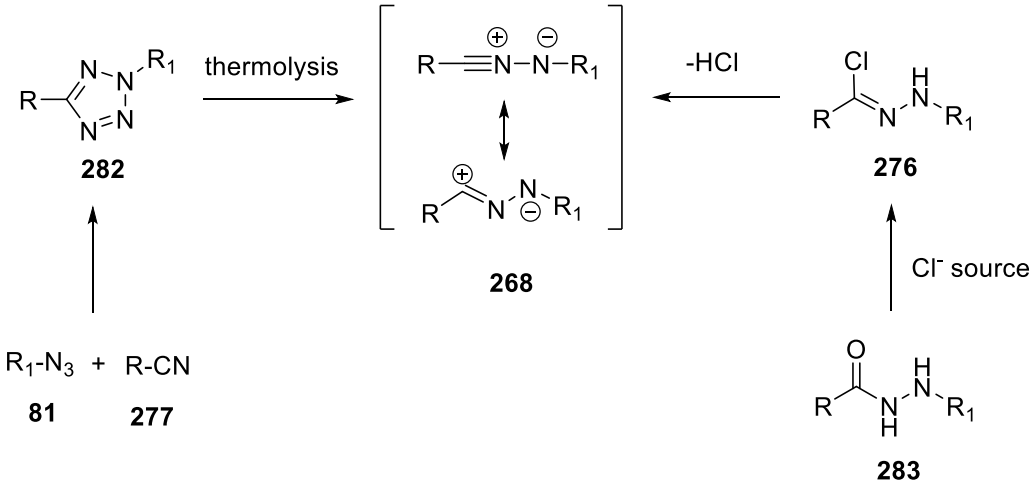


Scheme 3.4 Reactivity of nitrile imines

Although some stable nitrile imines have been isolated,[14] most of the nitrile imines have short half-life and hence are generated *in situ* from their precursors (Scheme 3.5). The first reported instance of nitrile imine generation by Huisgen involved the thermal breakdown of 2,5-

disubstituted tetrazole[6,15] (**282**)Simultaneously, he also reported the generation of nitrile imine by a base-induced dehydrohalogenation of hydrazonyl halides[5,16] (**276**). Over the years, hydrazonyl chlorides have proved to be more popular as a nitrile imine precursor as they are easy to synthesise, do not involve hazardous reagents (use of azide in tetrazole synthesis) or harsh conditions (thermolysis of tetrazoles). Hydrazonyl chlorides are readily accessible from different sources (ref), the most common being chlorination of aryl hydrazides (**283**) with PCl_5[17] or PPh_3/CCl_4[18] (Scheme 3.5).

Given that the generation of nitrile imines follows a similar path as that of nitrile oxide, we endeavoured to transfer our knowledge of nitrile oxide-cyanamide chemistry for the effective trapping of nitrile imine and cyanamide generated *in situ*. For this purpose, *N*-phenylbenzenecarbohydrazonyl chloride (**70**) was used as the nitrile imine precursor.



Scheme 3.5 Common methods for generation of nitrile imines

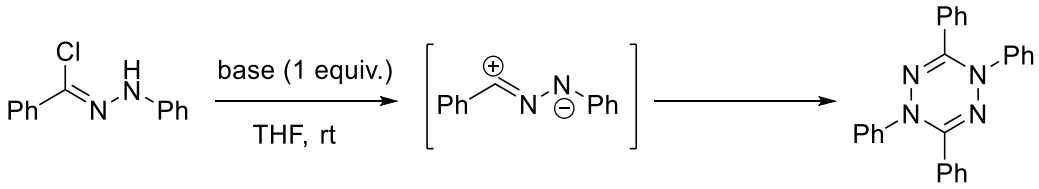
3.3 Generation of nitrile imine and its rate of formation

We decided to generate nitrile imine from hydrazonyl chlorides by a base-induced dehydrohalogenation. The use of base as well as fluoride source[19,20] for the generation of nitrile imine has been well-documented, with triethylamine as the base of 'choice'.[21] Similar to nitrile oxides, nitrile imines undergo a head-to-tail dimerisation in the presence of a base to give tetrazines (**281**). We decided to follow the rate of the nitrile imine generation by detecting the corresponding dimer formation.

Attempts to generate nitrile imine using triethylamine (1 mol equiv.) proved to be slow in the absence of a dipolarophile, as just 30% conversion was observed after 5 hours at room

temperature (GC-MS, entry 1, Table 3.1). Reactions involving triethylamine as the base often need long reaction times or reflux conditions. The reaction with TEA was performed to obtain the preliminary data for the dimer (**284**). The use of K_2CO_3 as the base did not return any dimer when reacted with N-phenylbenzenecarbohydrazonyl chloride (**70**) after 10 hours at room temperature (entry 2, Table 3.1).

Table 3.1 Study of the rate of formation of nitrile imine using different bases



70 **123** **284**

Entry	Base	Mol Equiv.	Time	% conversion[a]
1	Triethylamine	1	>5 h	30 %
2	K_2CO_3	1	>10 h	0 %
3	KF	1	2 h	10 %
4	CsF	1	2 h	40 %
5	CsF:18-C-6	1:1	1 h	100 %
6	CsF:18-C-6	1.5:1.5	10 min	100 %
7	KF:18-C-6	1.5:1.5	10 min	100 %
6	TBAF	1	5 min	100 %
7	*t*-BuOK	1	4 h	90 %

[a] monitored by GC-MS

Next, the alkali metal fluorides like KF and CsF were tested, which resulted in 10 % and 40 % conversion of **70** after 2 hours at room temperature (entry 3 and 4, Table 3.1). A combination of the F^- source with 18-crown-6 accelerated the reaction, as the starting material was consumed in 1 hour - 10 minutes (entry 5-7, Table 3.1). When 1 molar equivalent of TBAF

was used as the fluoride source, expectedly the reaction was completed in 5 minutes of the start of reaction (TLC and GC-MS, entry 6, Table 3.1). When compared with the rate of cyanamide ion formation (section **2.2.2**, Ch-2), TBAF and alkali metal fluorides/18-crown-6 seemed to generate the nitrile imine at a similar rate.

With these observations in hand, we decided to proceed towards screening these fluoride sources for the generation of both reactive species *in situ*, which is discussed below.

3.4 Preliminary studies for the *in situ* generation of nitrile imine and cyanamide ion

Initial screening for the *in situ* generation of nitrile imine and cyanamide ion from their corresponding precursors was started with TBAF as the fluoride source. It yielded a product with *m/z* 312 which was predicted to be 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-3-imine (**285**) (Figure 3.2).

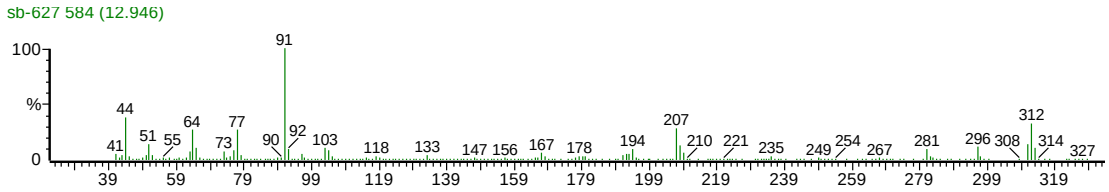
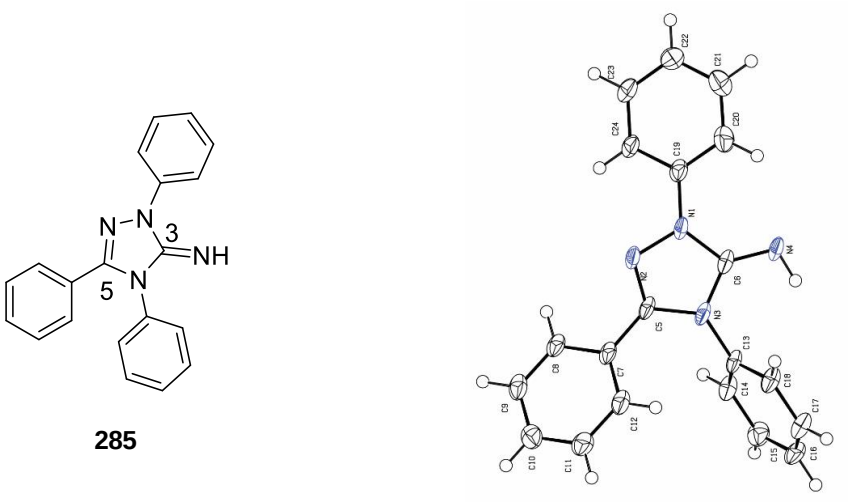


Figure 3.2 GC-MS spectrum of the main product **285** in the reaction of hydrazonyl chloride and NCTS with TBAF as fluoride source

The product obtained was a pale brown solid and readily soluble in water. The structure (Figure 3.3) was confirmed by NMR spectroscopic studies which displayed the presence of 15 aromatic protons with a broad singlet for N*H* at 4.48 ppm and a characteristic doublet at 8.12 ppm. The quaternary carbons C-5 and C-3 were assigned at 145.5 and 153.5 respectively in the ^{13}C NMR. The protons and the carbon were assigned with the help of DEPT, COSY and HSQC.

The IR spectrum for **285** showed a very strong band at 1629 cm^{-1} for the *exo*-cyclic C=N bond as well as a moderate band at 1590 cm^{-1} for the *endo*-cyclic C=N bond. These values were in accordance with those reported by Huisgen[3] - 1632 and 1564 cm^{-1} for the *exo*- and *endo*-cyclic C=N bond. In addition, HRMS (ESI) detected the $[M+H]^+$ mass of the 1,2,4-triazolimine and a final confirmation was achieved with the X-ray crystallographic analysis of a single crystal of **285**. Unlike 1,2,4-oxadiazol-5-imine compound, the compound 1,2,4-triazol-3-imine (**285**) was easily crystallised in ethyl acetate: petroleum ether system.



285

Figure 3.3 The structure and ORTEP diagram of 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-3-imine (**285**)

Interestingly, GC-MS analysis of the reaction mixture also showed the presence of a peak (Figure 3.4b) at 12.81 minutes along with the 1,2,4-triazol-3-imine peak at 12.95 minutes in a ratio of 3:7. A close mass to the product **285** with *m/z* 311 as M^+ ion peak and *m/z* 312 as M+1 ion peak, arose our suspicion if the new product is the heterocyclic isomer 1,2,4-triazole-amine (**286**). The product was difficult to isolate as the R_f value of this product overlapped with that of phenyl cyanamide (**104**). After much efforts, a toluene-acetone solvent system for the column purification yielded the new product in considerable purity.

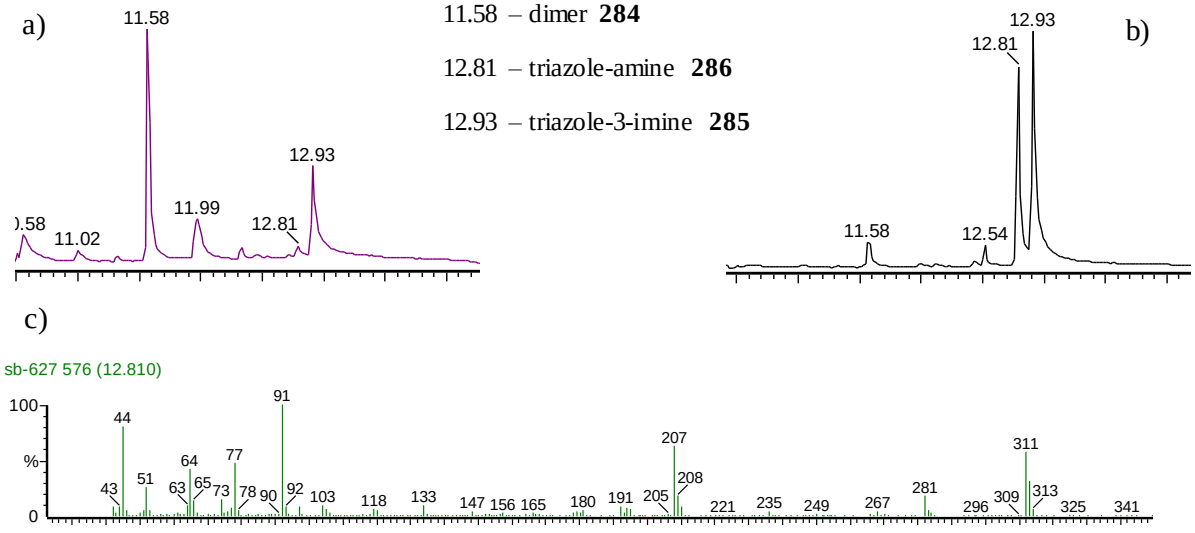
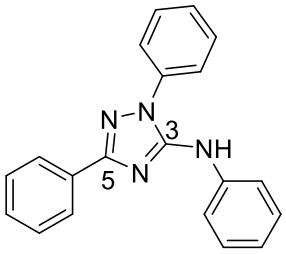


Figure 3.4 a) GC-MS chromatogram for the reaction spectrum, b) GC-MS spectrum for the new product at 12.81 minutes

The isolated product was analysed by NMR (^{1}H, ^{13}C, DEPT, COSY and HSQC) and IR spectroscopic studies. An apparent doublet at 8.20 ppm and a broad singlet at 6.45 ppm with the 15 aromatic protons in the region of 8.20-7.0 ppm was recorded on the ^{1}H NMR spectrum in $CDCl_3$. ^{13}C NMR spectrum showed signals for 5 quaternary carbons (triazole ring ^{13}C at 150.7 and 159.4 ppm) and 9 signals for methine protons which corresponds to 3 aromatic rings. IR spectrum showed two medium bands at 1598 and 1561 cm^{-1} and the HRMS detected the $[M+H]^{+}$ mass at 313.1451 (expected 313.1448 for $C_{20}H_{17}N_4$).



286

Literature Comparison

NH - 6.43 ppm

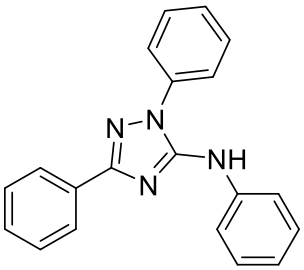
C-3 - 159.4 ppm

ArH- 8.20-7.0 ppm

IR: C=N - 1598 & 1561 cm^{-1}

Figure 3.5 Predicted structure for the new compound (**286**) with *m/z* = 312

With a view to confirm the structure, an exhaustive literature search for the 1,2,4-triazole-5-amine compound (**286**) was performed. Neugebauer *et al.* reported **286** as a thermolysis product of 1,2,4,5-tetrazine. The NMR signals for **286** were reported in the range of 1.8-3.2 τ (8.2-6.8 ppm) which matched the signals for the isolated compound (8.2-7.0 ppm). Zarguil and colleagues[23] reported a series of 1,2,4-triazole-amines with the NH proton at 6.3-6.4 ppm and IR absorption at 1560 cm^{-1} for the C=N. Further compounds with the main core of 1,2,4-triazole-amine were found[24,25] which showed specific signals for the quaternary carbon C-3 at 159.1-159.4 ppm and a C=N band (IR) at 1596 cm^{-1}.



286

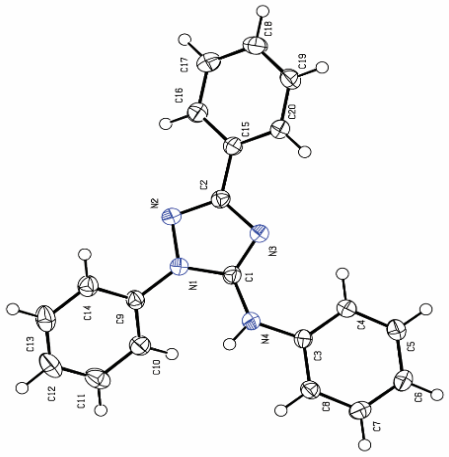
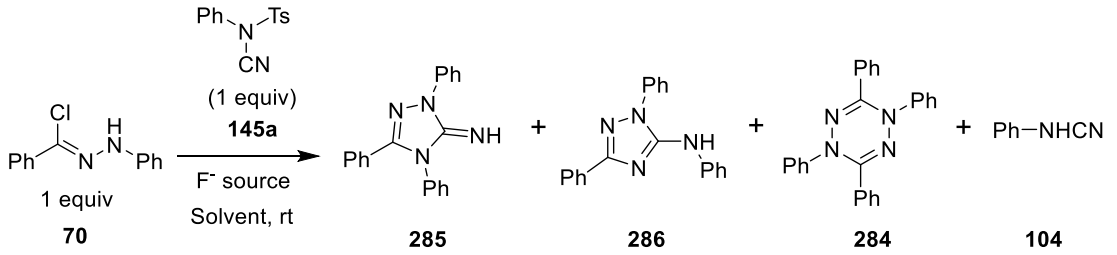


Figure 3.6 ORTEP diagram of 5-anilino-1,3-diphenyl-1,2,4-triazole (**286**)

The available data made a strong case for the isolated new compound to be **286**. The compound was confirmed finally by single crystal X-ray diffraction, the ORTEP drawing of which is shown in Figure 3.6. Having identified the three main products forming in the reaction, further optimisation with different fluoride source were carried out (Table 3.2).

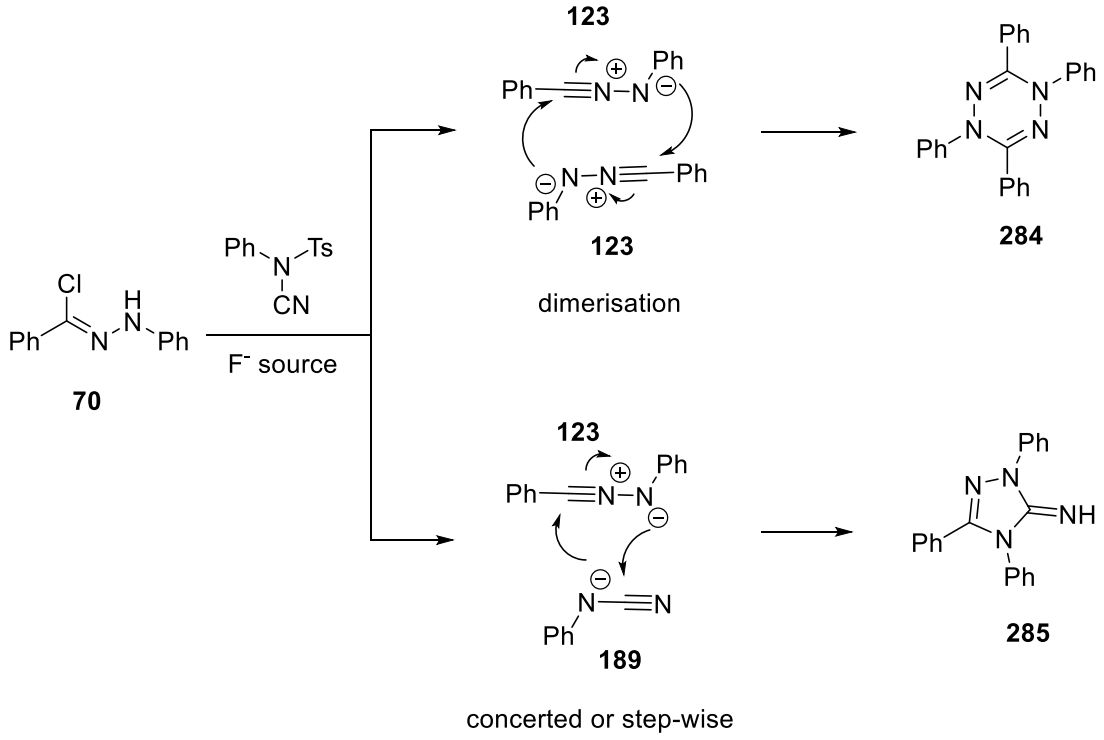
Table 3.2 Screening of F^- source for reaction between hydrazonyl chloride (**70**) and NCTS



Entry[a]	F^- Source	Mol Equiv.	Solvent	Time (min)	Yield **285**[b] (%)	Ratio[c] (**285**:**286**)	Ratio[c] (**285**:**284**)
1	TBAF	2	THF	10	13	55:45	18:72
2	TBAF	2	THF	15[d]	38	60:40	45:55
3	KF/18-C-6	2.5:2.5	CH_3CN	10	25	85:15	30:70
4	CsF/18-C-6	2.5:2.5	CH_3CN	10	46	65:35	55:45

[a] 0.21 mmol scale, [b] isolated yield, [c] calculated from NMR, [d] TBAF added slowly over a period of 15 minutes

As illustrated in Table 3.2, TBAF gave **285** in low yields. When 1 molar equivalent of N-phenylbenzenecarbohydrazonyl chloride (**70**) was reacted with NCTS (1 mol equiv.) in presence of TBAF (2 mol equiv.) in THF for 10 minutes at room temperature, it yielded the 1,2,4-triazol-3-imine (**285**) in a modest yield of 13 % with majority of the hydrazonyl chloride converted to its dimer **284**. As with the case of nitrile oxide-cyanamide reaction, we considered the slow addition of TBAF to suit the concomitant generation of both the reactive species. The slow addition of TBAF over a period of 15 minutes did result in an improved yield of 38 % (along with some minor impurities, more description in section 3.5). While the KF/18-crown-6 returned the product in just 25 % yield, an improved yield of 46 % was obtained for CsF/18-crown-6 in CH_3CN at room temperature (entry 3 and 4, Table 3.2).



Scheme 3.6 Competing formation of triazole-imine **285** and the nitrile imine dimer **284**

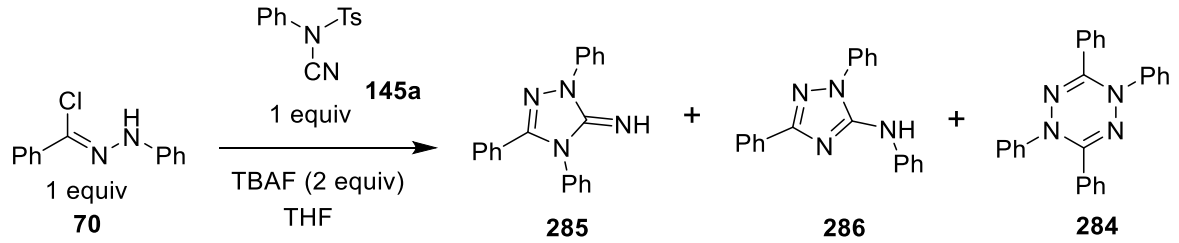
The major competing byproduct in the reaction between cyanamide ion and nitrile imine is the dimer (**284**, Table 3.2, Scheme 3.6) formed as a result of the head-to-tail dimerization of the nitrile imine.

With the aim to match the rate of formation of both reactive species, further optimisation with TBAF was carried out by changing the molar concentration of the reactants and their order and rate of addition. Adding 1 M TBAF (2 mol equiv.) and 0.5 M of **145a** dropwise to a 0.1 M solution of **70**, 51 % of triazole-imine was formed along with 45% of the dimer **284** (entry 1, Table 3.3). Changing the molar concentration to 0.5 M decreased the dimer formation considerably, but formed 38 % triazole-amine **286** instead (entry 2, Table 3.3). No dimer formation was observed when TBAF was added slowly (over 1 hour) and an improved **285**:**286** ratio of 62:38 was recorded (entry 3, Table 3.3). Performing the reaction at -78 °C, with TBAF added over a period of 15 minutes, lead to an increase in the dimer formation (63%) with lower ratios of imine **285** and amine **286** (entry 4, Table 3.3).

Although the dimer formation was eliminated in the reaction with TBAF, the triazole-amine (**286**) formation could not be controlled (entry 2 and 3, Table 3.3). Moreover, difficulties in the purification of the product from tetrabutylammonium impurities (described in section **3.6**)

prompted us to switch to a less basic fluoride source like CsF to optimise the nitrile imine-cyanamide ion cyclisation.

Table 3.3 Further optimisation with TBAF as the fluoride ion source



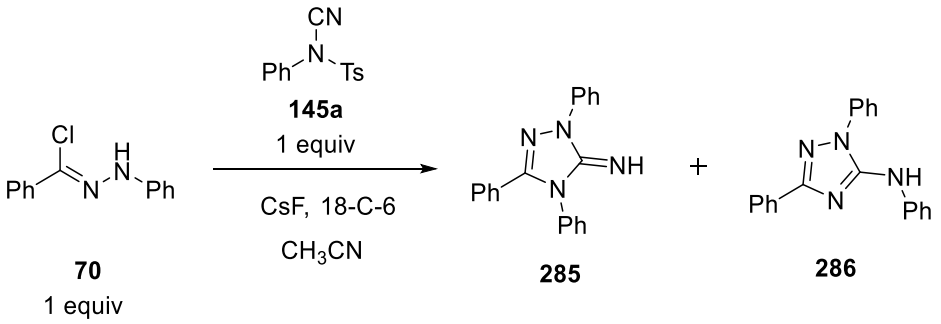
Entry[a]	Molar Conc. **70**:**145a**:TBAF	Order of addition	Time (min)	Temp	Ratio[b] **285**: **286**: **284**
1	0.1: 0.5: 1	TBAF and **145a** added dropwise	15	rt	51:4:45
2	0.5: 0.5: 0.5	TBAF and **145a** added dropwise	15	rt	54:38:8
3	1: 1: 1	TBAF added dropwise	60	rt	62:38:0
4	1: 1: 1	TBAF added dropwise	15	-78 °C	25:12:63

[a] 0.21 mmol scale, [b]ratio calculated using GC-MS

3.5 Optimisation with CsF as Fluoride source

As described earlier, an initial screening of CsF/18-crown-6 returned the 1,2,4-triazol-3-imine product (**285)** in 46% yield (entry 4, Table 3.2). Further optimisations with CsF/18-crown-6 were carried out to increase the yield of **285**, and thereby control the formation of the dimer and **286**. The stoichiometric changes in the CsF/18-crown-6 system resulted in a moderate to reduced product yield (entry 1-2, Table 3.4). With both the reactive species forming at a fast rate (<5 min), there was clearly a mismatch between the rate of generation of nitrile imine as well as cyanamide ion.

Table 3.4 Screening of CsF for the nitrile imine and cyanamide reaction



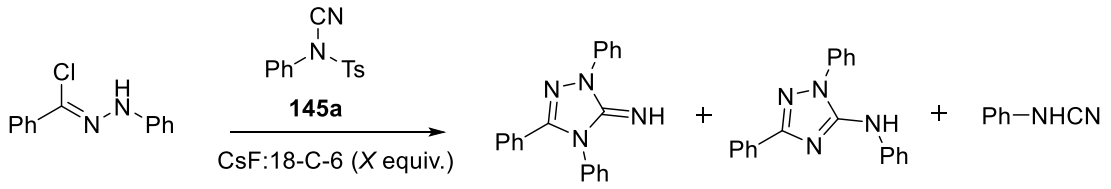
Entry[a]	Mol Equiv. CsF:18-C-6	Time (min)	Solvent	Temp	Yield **285**[b] (%)	**285:286**[c]
1	3.5:3.5	5	0.86 M	rt	46	64:36
2	3:4	2	0.43 M	rt	25	82:18
3	3.5:3.5	20	0.86 M	0 °C	25[d]	80:20
4[e]	3:3	30	0.86 M	0 °C	27	87:13
5[e]	3:3	30	0.17 M	0 °C	27	84:16

[a] 0.21 mmol scale, [b] isolated yields, [c] ratio calculated from the NMR of the crude reaction mixture, [d] 70% phenyl cyanamide was recovered [e] hydrazonyl chloride **70** was added to a reaction mixture containing **145a**, CsF and 18-C-6

Previous studies (chapter 2) have shown positive results when the reaction temperature was lowered down to 0 °C. The knowledge that the detosylation of NCTS slows down in ice-cold conditions, could provide a leverage point for further optimisations. Hence, when the reaction of *N*-phenylbenzenecarbohydrazonyl chloride (**70**) and NCTS (**145a**) was carried out in the presence of CsF/18-crown-6 at 0 °C, the hydrazonyl chloride (**70**) was completely consumed within 5 minutes, whereas NCTS remained unconsumed, giving a low product yield of 25%. Expectedly due to slower detosylation rate, around 70% of the phenyl cyanamide was recovered (entry 3, Table 3.4). Thus, the formation of nitrile imine was found to be faster than that of cyanamide ion at 0 °C.

In order to match the rate of formation at 0 °C, it was thought that by changing the order of addition of **70**, better yields could be obtained. So, hydrazonyl chloride was added to a reaction

Table 3.5 Slow addition of hydrazonyl chloride (**70**)- Screening with CsF/18-C-6



70 Slow addition — **285** — **286** — **104**

Entry	*X* equiv.	Additive	Solvent[a]	Time (min)[b]	Temp	Yield **285**[c] (%)	**285:286**[d]	Yield **286**, **104** (%)[c]
1	2.5:2.5	--	THF	60	rt	43	75:25	--
2	2.5:2.5		THF	120	rt	44	74:26	--
3	2.5:2.5	--	CH_3CN	60	rt	55	90:10	9[i]
4	2.5:2.5	MS 4 Å[e]	CH_3CN	60	rt	66	92:8	10[i]
5	2.5:2.5	Na_2SO_4[f]	CH_3CN	60	rt	52	92:8	12[i]
6	2.5:2.5	--	CH_3CN	60	0 °C	65	93:7	5, 20
7	3:3	--	CH_3CN	60	0 °C	63	80:20	16, 24
8	3:3	--	CH_3CN	30	0 °C	64	80:20	17,16
9	3:3	--	CH_3CN	15	0 °C	79	93:7	7,4
10[g]	3:3	--	CH_3CN[h]	20	0 °C	81	92:8	5, 4

[a] 0.86 M, [b] slow addition of **70** to a suspension of **145a**, CsF and 18-C-6, [c] isolated yields, [d] ratio calculated from the NMR of the crude reaction mixture, [e] 10 mol %, [f] 20 mol %, [g] **70** added after 10 minutes to a suspension of **145a**, CsF and 18-C-6, [h] 0.43 M, [i] isolated as a mixture

mixture containing **145a**, CsF/18-crown-6 in CH_3CN at 0 °C, but it resulted in just 27% of the desired product (entry 4, Table 3.4). Diluting the reaction mixture (0.17 M) did not affect the formation rates and gave similar product yields (27%, entry 5, Table 3.4).

Considering the faster generation of nitrile imine than the cyanamide ion, it was decided to add the hydrazonyl chloride (**70**) slowly to a mixture containing **145a**, CsF/18-crown-6 in a solvent. So, addition of **70** over a period of 1 hour to a reaction mixture containing NCTS, CsF/18-crown-6 with THF as the solvent, resulted in 43% product yield (entry 1, Table 3.5). The addition was next carried out over a period of 2 hours, which did not result in any significant change in the yield (44 % yield, entry 2, Table 3.5). The ratio of **285**:**286** was found to be 75:25, with rest of the hydrazonyl chloride (**70**) converted to the dimer. Changing the solvent polarity (CH_3CN) resulted in an increased yield of 55%, with an improved **285**:**286** ratio (entry 3, Table 3.5).

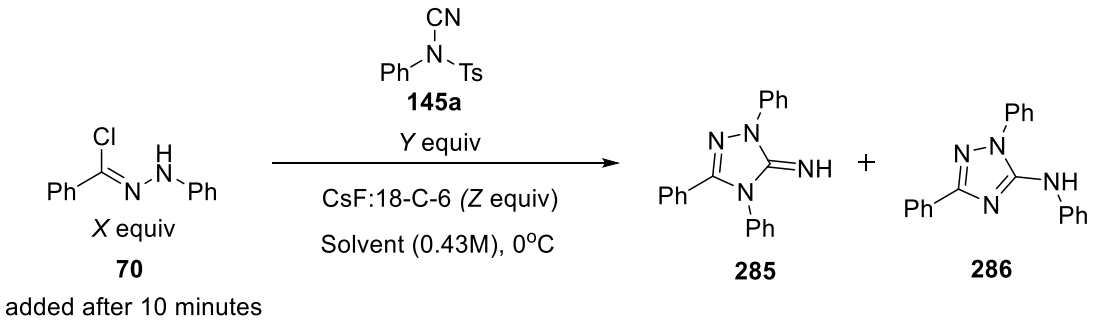
We reasoned that the triazole-amine (**286**) is forming due the availability of phenyl cyanamide (**104**) from the cyanamide ion (protonation). To verify this we thought to decrease the phenyl cyanamide formation via the use of molecular sieves (4 Å). An addition of 10 mol% molecular sieves resulted in an increased yield of 66%, with the phenyl cyanamide isolated in very low yields as expected (entry 4, Table 3.5). Although, the dimer formation also increased to 11% from 7%, indicating the acceleration of nitrile imine formation. When 20 mol% Na_2SO_4 was used, it reduced the yield of **285** to 52 % (entry 5, Table 3.5). When the reaction was tried in ice-cold conditions (same conditions as entry 3, Table 3.5) the yield was found to increase to 65% with a much improved ratio of 93:7 of **285**:**286** without the use of any additives (entry 6, Table 3.5).

The rate of addition of *N*-phenylbenzenecarbohydrazonyl chloride (**70**) was next controlled, which resulted in an increased yield of 79% when **70** was added over a period of 15 minutes (entry 9, Table 3.5), clearly indicating that both the reactive species are formed in the first 15 minutes of addition of the respective starting materials **1** and **2.** Based on the above results and previous observation, it was evident that nitrile imine forms within 5 minutes whereas the cyanamide anion forms over a period of 15-20 minutes at 0 °C.

To avoid using slow addition protocol, hydrazonyl chloride **70** was added after 10 minutes of the addition of CsF/18-crown-6 to NCTS at 0 °C. TLC showed complete consumption of both the starting materials after 20 minutes (total, after 10 minutes of addition of **70**). The reaction yielded the desired triazole-imine product (**285**) in 81% yield with a 92:8 ratio of imine **285**:

amine **286** (entry 10, Table 3.5). The reaction was diluted to 0.43 M as the reaction mixture formed a thick paste which impeded the stirring.

Table 3.6 Stoichiometry and solvent-screening with CsF/18-C-6 as fluoride source



Entry[a]	*X* equiv.	*Y* equiv.	Z equiv.	Solvent	Time (min)[b]	Yield **285**[c] (%)	**285:286**[d]
1	1	1	3:3	CH_3CN	20	81	92:8
2	1	1	2.5:2.5	CH_3CN	20	82	94:6
3	1.25	1	2.75:2.75	CH_3CN	20	66	77:23
4	**1**	**1.25**	2.75:2.75	**CH_3CN**	**20**	**89**	**94:6**
5	1	1.25	2.75:2.75	CH_2Cl_2	20	82	90:10
6	1	1.25	2.75:2.75	DMF	20	61	86:14
7	1	1.25	2.75:2.75	THF	90	45	55:45
8	1	1.25	2.75:2.75	Toluene	90	49	67:33

[a] 0.21 mmol scale, [b] total time, [c] isolated yields, [d] calculated from crude NMR

With excess of fluoride source being used in the reaction, the reaction was attempted with 2.5:2.5 molar ratio of CsF:18-crown-6, which returned similar product yields (82%, entry 2, Table 3.6). An increase in the molar equivalent of **70** resulted in decreased yield of 66%, whereas using 1.25 molar equivalents of **145a** increased the yield to 89% with 94:6 ratio of **285**:**286** (entry 4, Table 3.6).

Solvent screening was performed with the optimised stoichiometry of the reagents (entry 4, Table 3.6). The use of DCM gave a similar product yield as with CH_3CN, whereas lower yields were recorded with DMF as the solvent (entry 5-6, Table 3.6). Changing the solvent to THF, resulted in a significant reduction in the product yield (45%), with a prominent increase in the formation of **286** (entry 7, Table 3.6). The reaction was found to be sluggish when toluene was used as a solvent, as both the starting materials remained unconsumed even after 90 minutes (TLC), resulting in inferior product yields (49%, entry 8, Table 3.6).

Thus, optimal results were obtained by the late addition (10 min) of the hydrazonyl chloride (**70**) to a reaction mixture containing **145a** and CsF/18-crown-6 (2.75:2.75 mol equiv.) in CH_3CN at 0 ^oC, with a total reaction time of 20 min (entry 4, Table 3.6).

3.6 Investigating the substrate scope

3.6.1 Synthesis of hydrazonyl chlorides

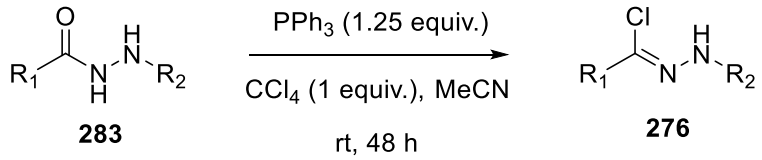
Following the successful result obtained with *N*-phenylbenzenecarbohydrazonyl chloride (**70**), we were keen to investigate the reactivity of other nitrile imines (**268**) with NCTS (**145a**) under these optimised conditions. Therefore, several hydrazonyl chloride derivatives were synthesised bearing electron-withdrawing, electron-donating, heteroaryl and aliphatic groups. Also, *o*-substituted nitrile imines were synthesised, as these are known to stabilise nitrile imines and give comparable yields to **70**. The hydrazonyl chlorides were synthesised using a number of different methods reported in literature.

3.6.1.1 Chlorination of acyl hydrazides

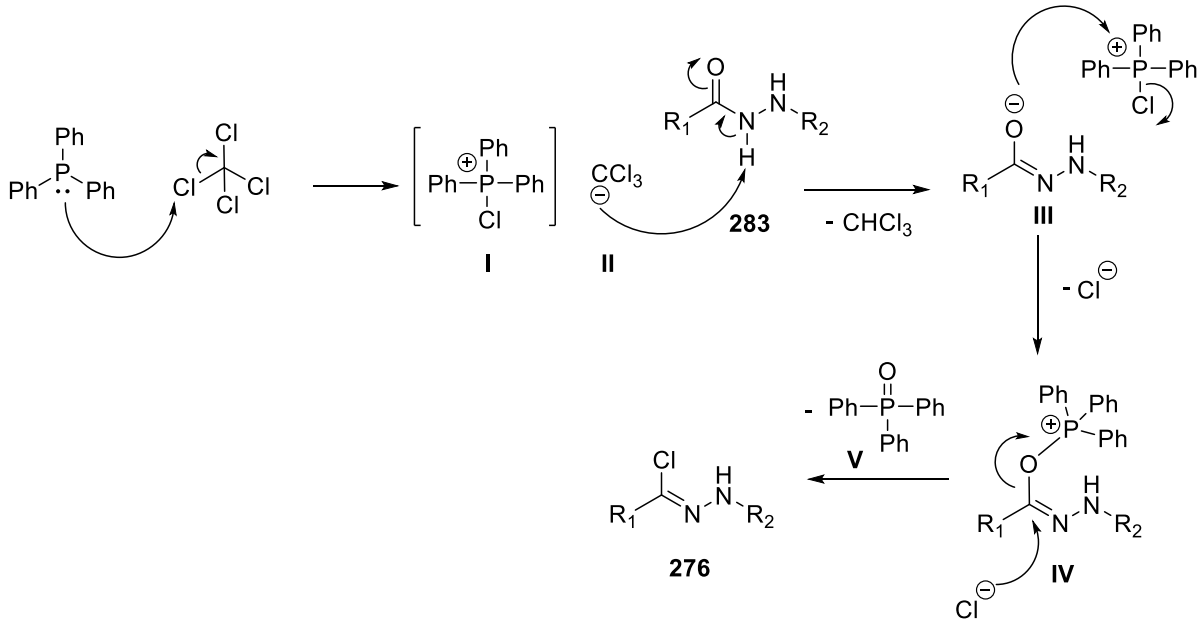
Several chlorinating agents have been used for the chlorination of acyl hydrazides. A triphenylphospine and carbon tetrachloride (PPh_3/CCl_4) [18] system was used wherein CCl_4 was added to a suspension of aryl hydrazides and PPh_3 in MeCN and allowed to stir at room temperature (Scheme 3.7). The precipitates formed were filtered and recrystallised or purified by silica gel column chromatography, giving the hydrazonyl chlorides (**70, 290-299**) in varying yields (Figure 3.7).

The reaction begins with the formation of phosphonium salt (**I**, Scheme 3.8), which is thought to exist as a tight ion-pair with **II**. Deprotection of the aryl hydrazide by the CCl_3^- ion (**II**, Scheme 3.8) forms chloroform and yields an alkoxide (**III**). The nucleophilic substitution of chloride in the phosphonium salt (**I**) by the alkoxide yields an oxyphosphonium intermediate

(**IV**). The chloride ion attacks the C-centre in **IV** via a S_N2 process forming the hydrazonyl chloride (**276**) and triphenylphosphine oxide (**V**, TPPO). The formation of triphenylphosphine oxide and the strong P=O bond is considered the driving force in this reaction (Scheme 3.8).

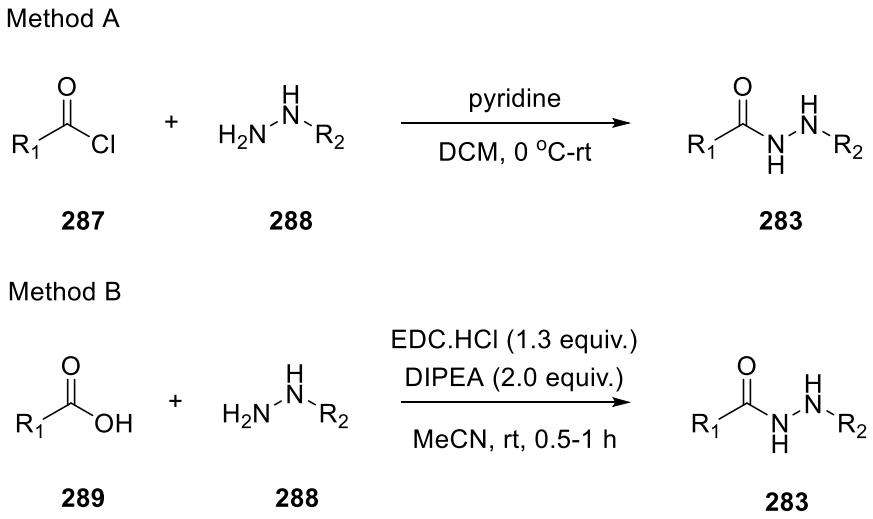


Scheme 3.7 Synthesis of hydrazonyl chlorides (**276**) from aryl hydrazides (**283**)



Scheme 3.8 Mechanism for the formation of hydrazonyl chlorides (**276**)

The aryl hydrazides were in turn synthesised using two different methods from the literature, method A and method B (Scheme 3.9). In method A, the corresponding acyl chloride (**287**, 1.0 mol equiv.) was added dropwise to a solution of hydrazine derivative (**288**, 1.0 mol equiv.) and pyridine (1.0 mol equiv.) in DCM at 0 °C. The reaction mixture was left to warm up slowly to room temperature and monitored by TLC. After the completion of the reaction, the solids were filtered off, washed and recrystallised from ethanol to give the desired aryl hydrazides (**283**) in high purity and in good yields. Only **70** was synthesised using this procedure. The rest of the acyl hydrazides were preferred to be synthesised by method B.



Scheme 3.9 Synthesis of aryl hydrazides from A) acyl chlorides **287**, B) carboxylic acids **289**

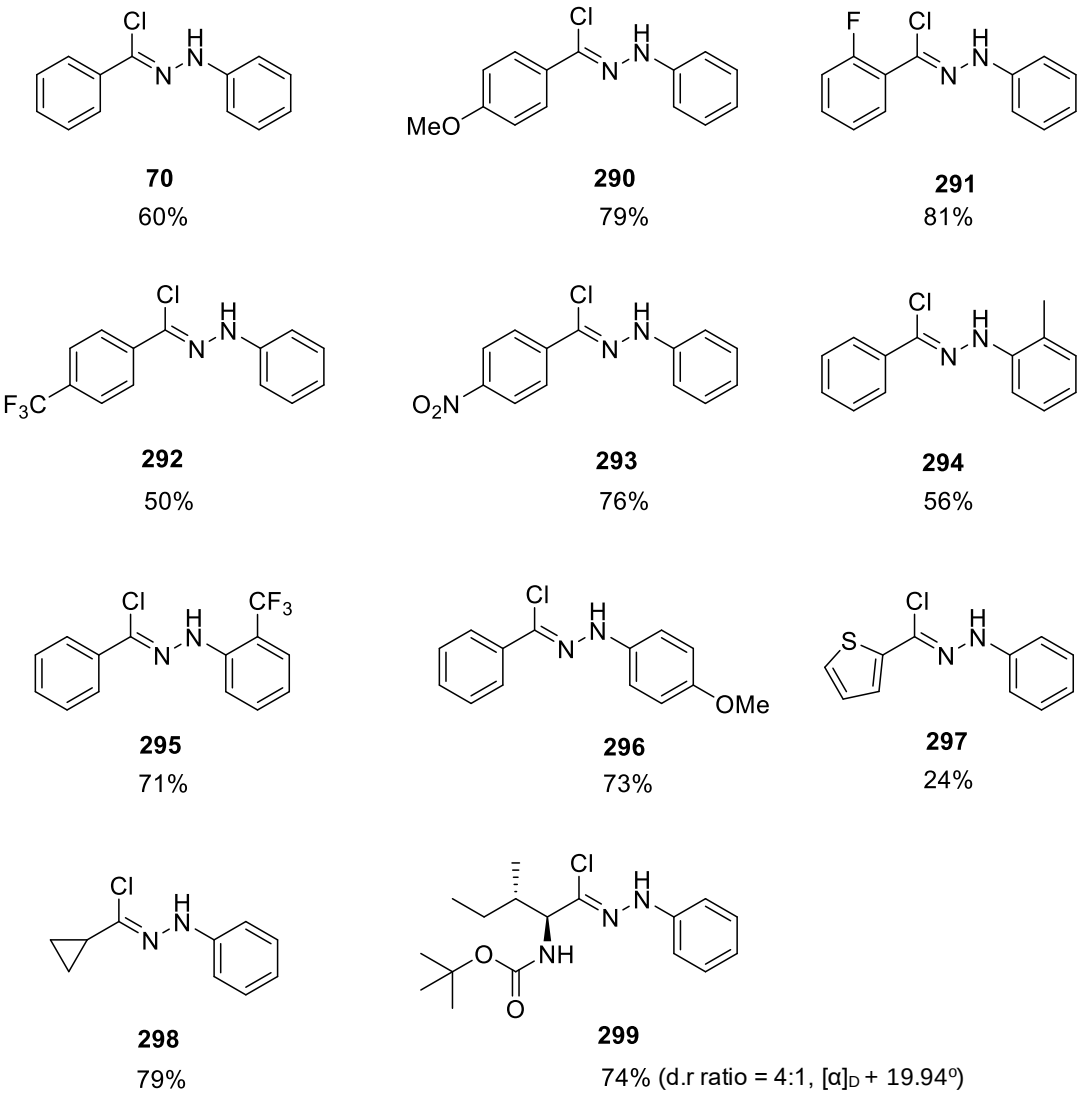


Figure 3.7 Hydrazonyl chlorides synthesised from aryl hydrazides

According to a report,[26] products derived from hydrazine salts (commercially available form) were obtained in lower yields using method A, as bis-acylation was found to be more favoured over mono-acylation. To overcome this drawback, less reactive acylating agents were used, which was adopted here in the form of method B (Scheme 3.9B). Method B involved the addition of DIPEA (2.0 mol equiv.) to a solution of hydrazine derivative (**288,** free or as HCl salt), carboxylic acid (**289**, 1.0 mol equiv.) and *N*-(3-Dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride **(**EDC.HCl, 1.3 mol equiv.) in MeCN at ambient temperature. The reaction was left to stir until completion (TLC). The reaction mixture was then worked up and the crude product was carried forward either as it is or in some cases purified by silica gel column chromatography. The products **300**-**310** were obtained in good yields (Figure 3.8).

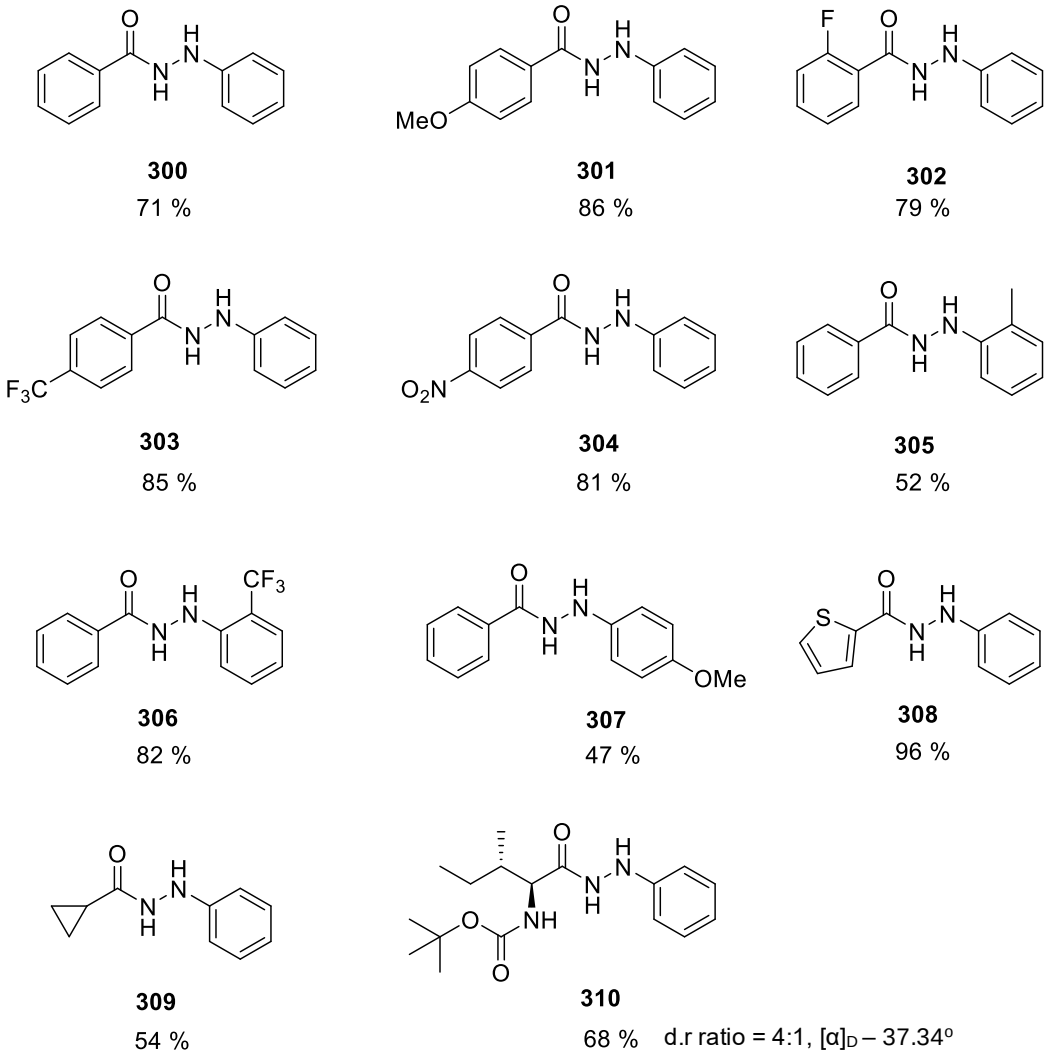
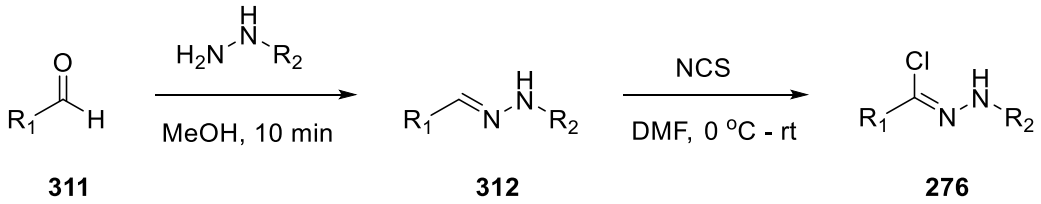


Figure 3.8 Aryl hydrazides synthesised using method B

3.6.1.2 Chlorination of aryl hydrazones

For the synthesis of the corresponding boc-protected hydrazonyl chlorides **313-315**, we employed a method reported by Pramanik et.al,[27] where in NCS-DMF was used for chlorinating the hydrazones. While NCS has been used for the chlorination of oximes, the chlorination of hydrazones has been only reported using NCS-dimethylsulfide complex in DMF at -78 °C.[28] We tried to replicate the method by Pramanik *et al.* by condensing aromatic aldehydes **311** with tert-butyl carbazate to yield the corresponding hydrazones **312**, which was successfully chlorinated using NCS/DMF to give the hydrazonyl chlorides **313-314** in varying yields (Scheme 3.10, Figure 3.9). 2-Pyridine carboxaldehyde and 3-furancarbaldehyde also gave the corresponding hydrazonyl chlorides (**315-317**) in good yields using the above protocol (Figure 3.9)



Scheme 3.10 Synthesis of hydrazonyl chlorides from aldehydes

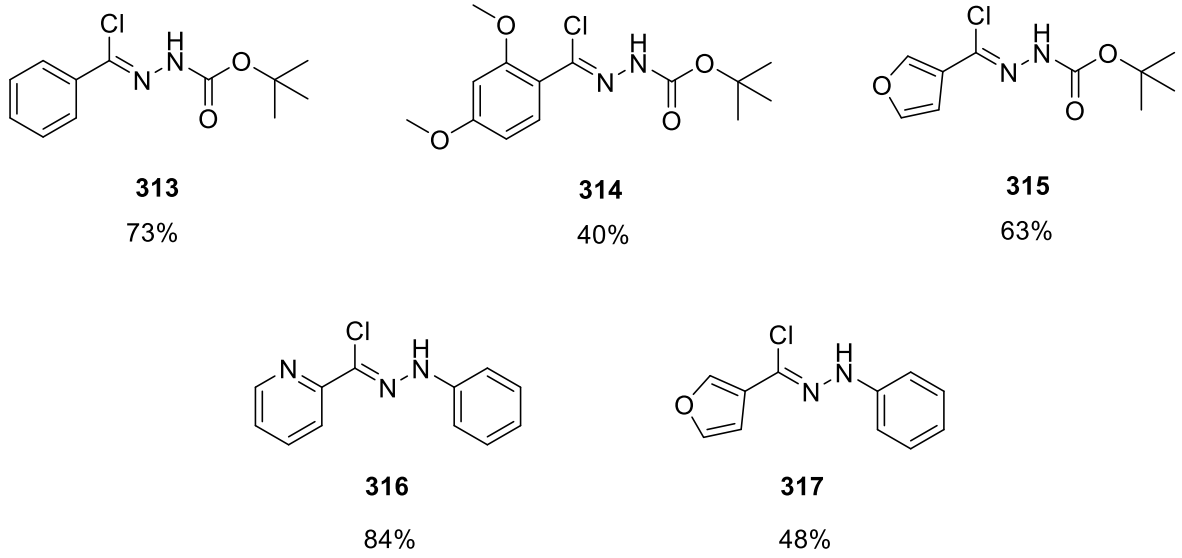
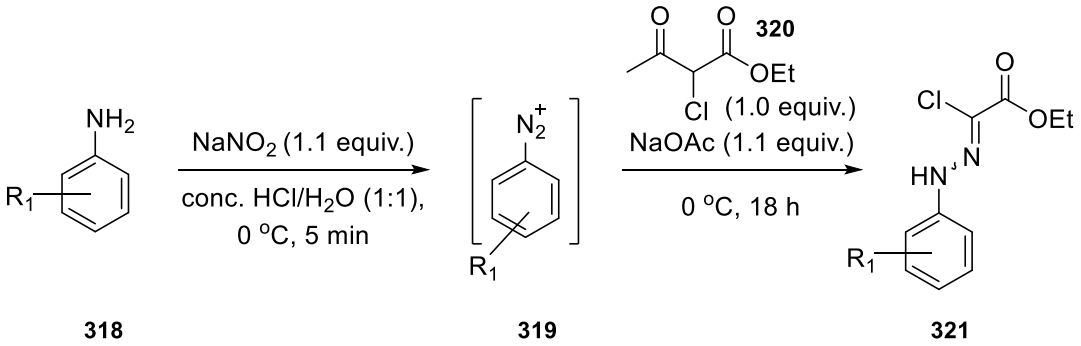


Figure 3.9 Hydrazonyl chlorides **313-317** synthesised from aromatic aldehydes

3.6.1.3 Japp-Klingemann synthesis

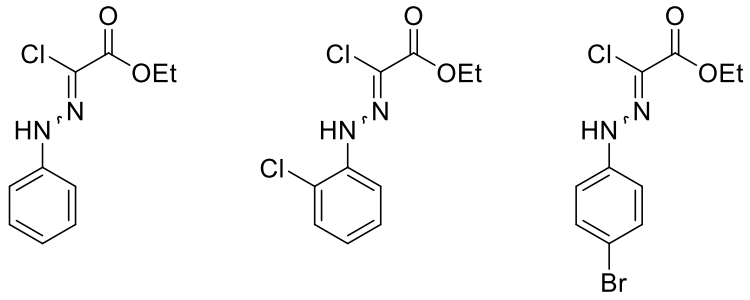
In order to synthesise alkyl ester derivatives of hydrazonyl chlorides, Japp-Klingemann reaction[29] was employed. The aryl diazonium salt was generated *in situ* by adding a solution of aniline (14, 0.02 mol) in dilute HCl (1:1, 8 mL) to $NaNO_2$ (1.1 mol equiv.) in H_2O (10 mL) under ice-cold conditions over a period of 5 minutes (Scheme 3.11).



318 **319** **321**

Scheme 3.11 Japp-Klingemann synthesis of hydrazonyl chlorides from diazonium salts

The diazonium solution was immediately added dropwise to a solution containing sodium acetate and commercially available ethyl 2-chloro-3-oxobutanoate (**320**) to yield the hydrazonyl chlorides **321a-c** in good to excellent yields (Figure 3.10).



321a 91 %

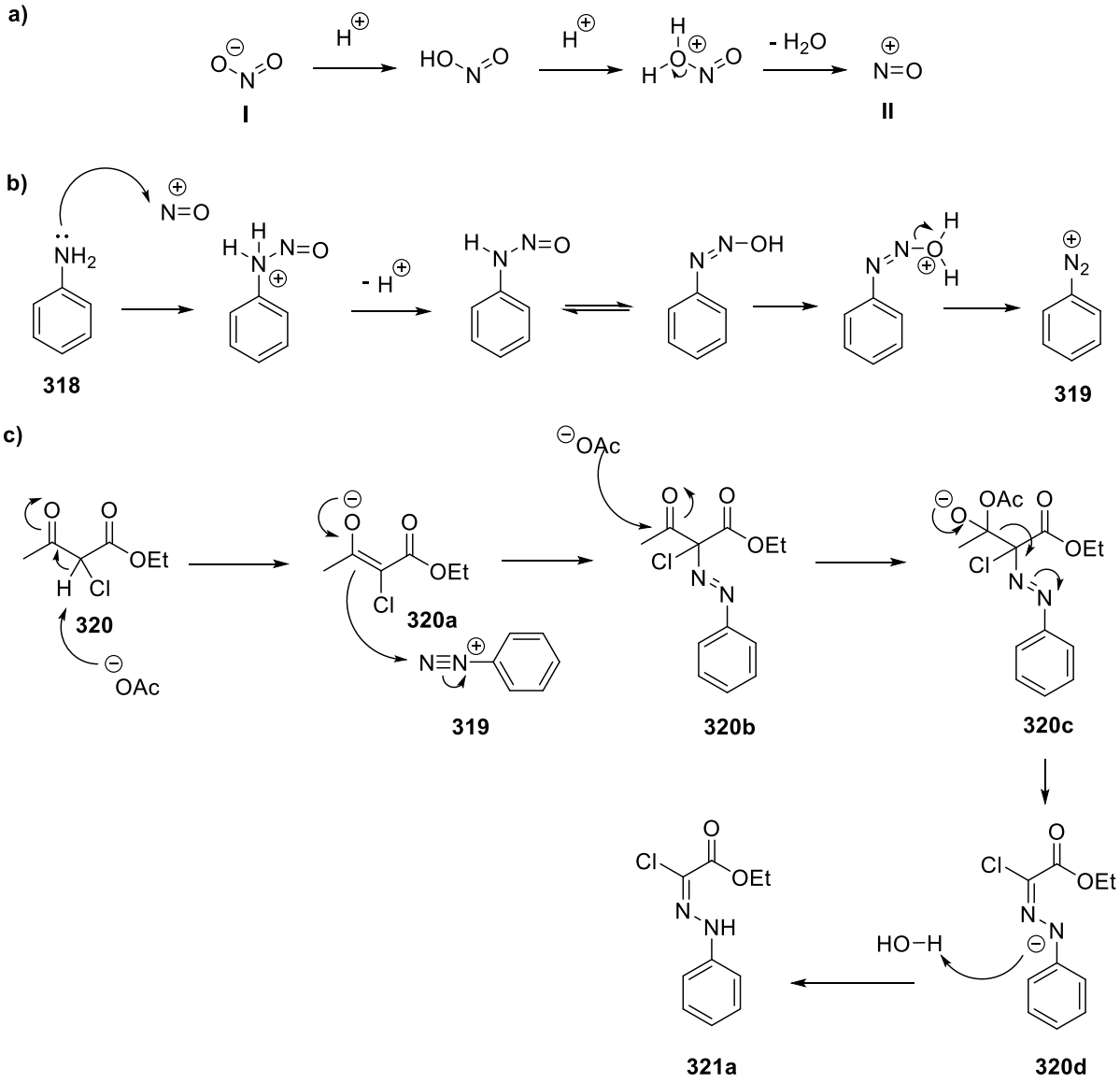
321b 87 %

321c 96 %

Figure 3.10 Hydrazonyl chlorides synthesized by Japp-Klingemann synthesis

The mechanism for the Japp-Klingemann synthesis is shown in scheme 3.12. The nitrosonium cation (NO^+) present in the acidic nitrous acid solution reacts with aniline to form the aryl diazonium salt **319** (Scheme 3.12a and 3.12b). In another solution, the acetate ion is involved in the deprotonation of the β-keto-ester (**320**) forming an enolate **320a** (Scheme 3.12c). The nucleophilic addition of the enolate anion to the diazonium salt produces the azo compound **320b**. The nucleophilic attack of the acetate anion at the carbonyl centre of **320b** produces a

tetrahedral intermediate **320c**, which quickly decomposes to release the carboxylic acid ester and form **320d**. After hydrogen exchange, the final hydrazonyl chloride (**321a**) is produced (Scheme 3.12c).



Scheme 3.12 Mechanism for Japp-Klingemann synthesis of hydrazonyl chloride (**321**)

3.6.2 Substrate Scope

Various nitrile imine precursors were investigated including **290-299**, **313-317**, **321a-c** towards the construction of the target triazol-3-imines. The results are illustrated in Table 3.7. The protocol was found to tolerate a wide range of functionalities, including aryl, aliphatic and heterocyclic substituted carbahydrazonyl chloride (entries 1-20, Table 3.7).

The triazol-5-amines (**286, 322'-340'**) were also detected along with the target triazole-3-imines. The ratio of triazole-3-imine: triaozol-5-amine was calculated from the NMR of crude reaction mixture (Table 3.7).

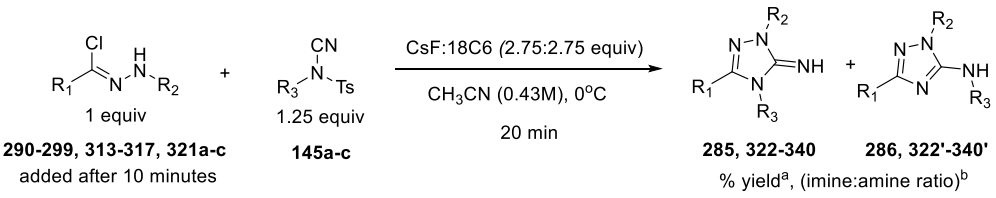
All the products obtained were isolated by silica gel column chromatography and characterised by NMR (^{1}H, ^{13}C, DEPT, COSY and HSQC), IR and HRMS. Hydrazonyl chlorides bearing electron-donating as well as electron withdrawing aryl groups on the R^1 were well tolerated with yields raning from 76 – 86 % (**322-325**, Table 3.7). Change in the electronics on R^2 had a substantial effect on the efficiency of the reaction, as *p*-methoxy aryl group gave excellent yield (**328**, 83 %), whereas electron-withdrawing group caused a decrease in the yield (**326**, 44%). This is in accordance with a study by Qing Lin *et al.*[30] who suggested the role of electron-donating groups on R^2 in lifting the HOMO energy of the dipole, as well as lowering of E_{HOMO} due to the presence of electron-withdrawing groups. The hypothesis was supported by both experimental rate constants as well as theoretical calculations of the energy of the nitrile imine species.

Furthermore, the sterically hindered nitrile imines gave the 1,2,4-triazol-3-imines in moderate yields only (**326-327**, 44%). The introduction of electron-poor cyanamides lead to poor yields (**329**, 44 %), with electron-rich cyanamides giving moderate yields (**330**, 61 %). Furthermore, combination of electron-rich nitrile imine and electron-poor cyanamide and vice versa gave good yields of the 1,2,4-triazoleimine product (**331**, 71% & **332**, 78%). Hydrazonyl chlorides bearing heterocycles, such as thiophene (**297**) and pyridine (**316**) were well tolerated (entries 13 and 14, Table 3.7), giving **333** and **334** in 85 % and 70 % yield respectively. Aliphatic hydrazonyl chlorides bearing cyclopropyl, alkyl esters as well as *NH*-boc protected alkyl groups gave good product yields (**335, 337-340**, 58-82%).

The *N*-(tert-butoxycarbonylamino)-phenylhydrazonoyl chloride **313** gave 3,4-diphenyl-1,2,4-triazole-3-imine **336** in 62% yield after silica gel column purification (the acidic silica gel caused the boc-removal from *N*-1 of the triazole-imine), saving the further step of boc-deprotection. The triazole-imine **336** with a free NH (*N*-1) could be functionalised by introduction of alkyl, alkyl-ester, alkyne or aromatic groups providing handles for further functionalisation.

The other *N*-boc protected aromatic hydrazonyl chlorides **314** and **315** failed to give the desired product, as the nitrile imine could not be generated in both the cases.

Table 3.7 Substrate scope of the nitrile imine- cyanamide ion cyclisation

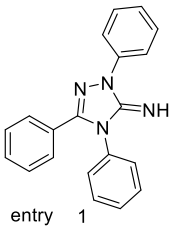
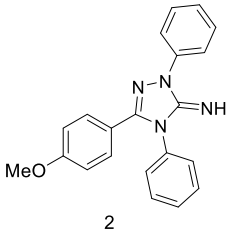
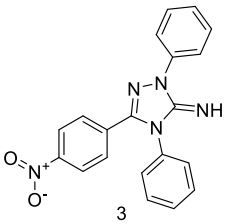
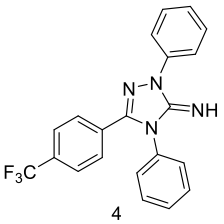
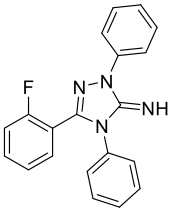
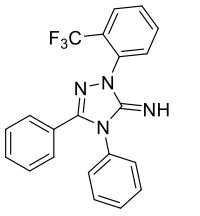
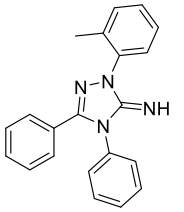
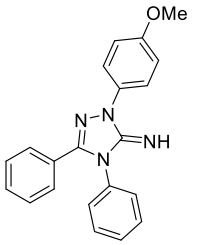
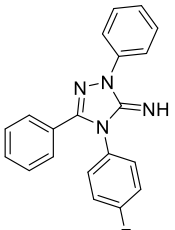
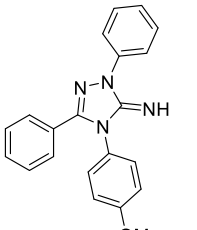
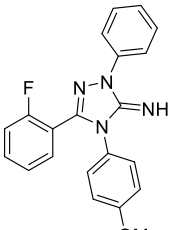
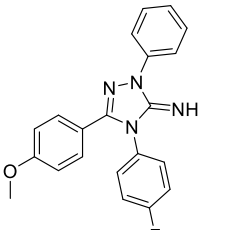
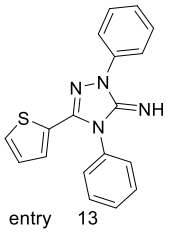
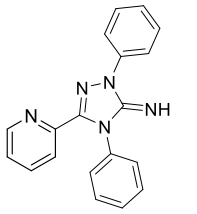
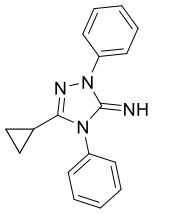
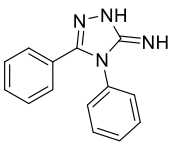
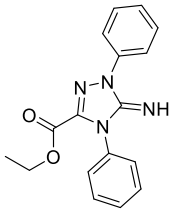
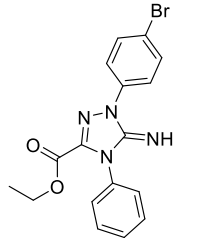
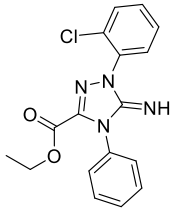
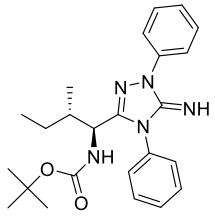


1 equiv — 1.25 equiv

290-299, 313-317, 321a-c added after 10 minutes — **145a-c**

285, 322-340 — **286, 322'-340'**

% yield[a], (imine:amine ratio)[b]

				
entry 1	2	3	4	
285, 89 % (96:4)[b]	**322**, 86 % (95:5)	**323**, 76 % (93:7)	**324**, 81 % (91:9)	
				
entry 5	6	7	8	
325, 81 % (96:4)	**326**, 44 % (92:8)	**327**, 44 % (-)[c]	**328**, 83 % (92:8)	
				
entry 9	10	11	12	
329, 44 % (81:19)	**330**, 61 % (92:8)	**331**, 71 % (91:9)	**332**, 78 % (94:6)	
				
entry 13	14	15	16	
333, 85 % (93:7)	**334**, 70 % (88:12)	**335**, 58 % (91:9)	**336**, 62 % (-)[c]	
				
entry 17	18	19	20	
337, 82 % (92:8)	**338**, 71 % (94:6)	**339**, 60 % (92:8)	**340**, 61 % (90:10) $[\alpha]_D - 41.55^o$	

[a]Isolated yield by column chromatography, [b]ratio determined by NMR, [c]undifferentiable peaks

3.7 Workup and Isolation of the 1,2,4-triazol-3-imine compounds

As the target compound was found to be water-soluble, an aqueous workup to get rid of excess of TBAF was not possible. Hence, Dowex H^+ resin along with $CaCO_3$ was used to remove the tetrabutylammonium impurities,[31] but complete removal of the TBA impurities could not be achieved (1:18 of **285**: TBAF went down to 1:9). Also, using the Dowex ion exchange resin to trap the product in exchange of H^+, and finally eluting the product with ammonia did not offer clean product. The TBA impurities did not get completely washed off the resin and co-eluted with product during ammonia wash. In the total synthesis of fulicinerine,[32] the reaction mixture after TBAF-mediated desilylation was taken in diethyl ether and washed with sat. aq. ammonium chloride (NH_4Cl) to get rid of the tetra butyl ammonium impurities as a chloride salt. Using a similar approach, when the reaction mixture was washed with aq. NH_4Cl, the product was obtained in considerable purity (but with minor TBA peaks in NMR).

With the CsF/18-crown-6 system, the purification of the product from the 18-crown-6 impurities posed a problem. Considering the aqueous solubility of the product, direct loading of the reaction mixture on a silica gel column was tried, but it resulted in the elution of 18-crown-6 along with the product.

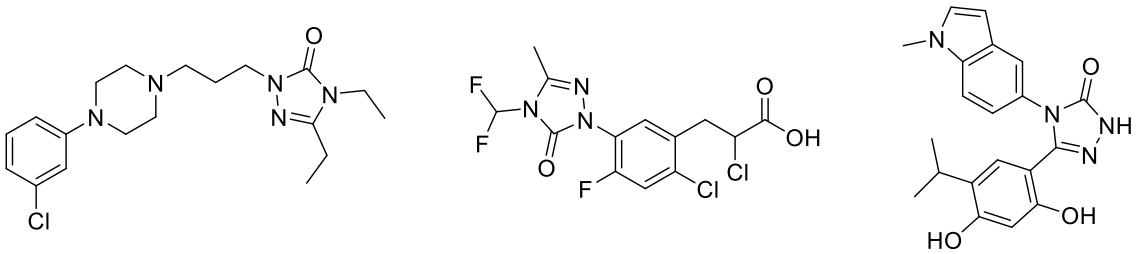
Forming a hydrochloride salt of the product **285**, did not yield the pure product as 18-crown-6 impurities were present. Finally, washing the reaction mixture with sat. aq. potassium chloride (KCl) thrice helped in removing all the 18-crown-6 impurities, and pure product was isolated after silica gel column chromatography.

3.8 Post-functionalisation of 1,2,4-triazol-3-imines: Synthesis of 1,2,4-triazole-3-ones

1, 2, 4-triazol-3-ones are important heterocyclic cores found in many leading drugs candidates for example, etoperidone (anti-depressant), itraconazole (anti-fungal) and herbicides like carfentrazone, benzcarbazone, etc. (Figure 3.11). They also show a broad spectrum of biological activities such as antivirals, anti-microbials, anti-hypertensives, anti-inflammatory, anti-obesity (CB1 selective anatognist) and fungicidals.[33]

Ganetepsib (**343**), a triazolone containing investigational drug molecule is a small-molecule heat shock protein 90 (Hsp90) inhibitor, being developed for treating multiple solid tumor and hematologic cancers. In *in-vitro* and *in-vivo* models, ganetespib has shown potent activity

against a wide range of cancer types, including lung, prostate, colon, breast, gastric, pancreatic, gastrointestinal stromal tumors, melanoma, acute myeloid leukemia, chronic myeloid leukemia, Burkitt's lymphoma, etc., and also in Phase II clinical trials as a combination with other drugs (with Paclitaxel for ovarian cancer, with dutasteride for hormone resistant prostrate cancer, with fulvestrant for metastatic breast cancer.



341

etoperidone
(anti-depressant)

342

carfentrazone
(herbicide)

343

ganetespib
(Hsp90 inhibitor)

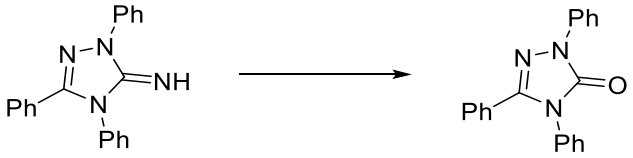
Figure 3.11 1,2,4-triazolone containing pharmaceuticals and agrochemicals

It has also been used as a drug conjugate for targeted delivery of topoisomerase I inhibitors to tumours. Various methods exist to synthesise the 1,2,4-triazolone ring, the most common involving a cyclisation-dehydration sequence of acyl semicarbazides in alkaline solutions, reaction between 1,2,4-triazolium salts with aqueous potassium carbonate, the condensation of mono Boc-protected hydrazines with acyl isocyanates and the subsequent deprotection and then an intramolecular cyclisation of the intermediate, a reaction of amidrazones and isocyanate esters and the cyclisation of the imidoylsemicarbazide of ethyl chloroformate and *N*-1-tosylamidrazones, the cyclisation of 1-aryl-1 nitroso-3-(2-pyridylmethyl) ureas and a reaction between thiocarbohydrazide and substituted benzoyl hydrazine.

The hydrolysis of 1,2,4-triazol-3-imine could provide an alternative route towards the pharmaceutically important 1,2,4-triazolone core. Following our success with the acidic hydrolysis of 1,2,4-oxadiazol-5-imines **177** to 1,2,4-oxadiazol-5-ones **178**, we followed the protocol by refluxing **285** in the presence of conc. HCl in MeOH, which did not yield any product (entry 1, Table 3.8). The use of trifluoroacetic acid returned the starting material, whereas under alkaline conditions (KOH, *t*-BuOK) which included heating microwave conditions (220 ^{o}C) did not afford any hydrolysed product 1,2,4-triazoleimine (entry 2 and 3, Table 3.8).

Alper and Baeg[34] utilised 5 % sodium hypochlorite under phase transfer catalysis conditions for the hydrolysis of imidazolidenimine to the correspinding imidazolidinone in 57% yield (JOC, 1992). Utilising similar conditions – 10% sodium hypochlorite and tetra-*n*-butyl ammonium hydrogen sulfate in chloroform gave only 10% yield of 1,2,4-triazolone **345** after 24 hours (entry 4, Table 3.8).

Table 3.8 Hydrolysis of 1,2,4-triazol-3-imine



285 **345**

Entry	Reagents	Solvent	Temp	Time (h)	Yield (%)[a]
1	Conc. HCl	MeOH	reflux	24	0
2	Trifluoroacetic acid	MeOH	reflux	24	0
3	KOH, *t*-BuOK (3:3)	THF	rt[b]	24	0
4	10% NaOCl, $Bu_4N^+HSO_4^-$	$CHCl_3$	rt	24	10
5	$NaNO_2$, $NaOOCCH_3$	50% CH_3COOH	0 °C- rt	6	76

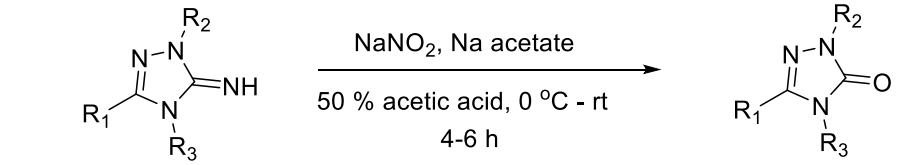
[a] Isolated yield, [b] also heated in microwave at 220 °C for 10 minutes in toluene

A system comprising of sodium nitrite and sodium acetate in 50% acetic acid gave the desired product **345** in good yield of 76%. The reaction is known to produce nitrous acid *in situ*, which is responsible for the hydrolysis of the 1,2,4-triazolimines **285**. The method was adopted from Huisgen's earlier reported findings on 1,2,4-triazol-3-imine.[3] In this method, slow addition of sodium nitrite to a solution of **285** and sodium acetate in 50% acetic acid at 0-5 °C was crucial. The reaction was allowed to come to room temperature slowly and stirred for 4-6 hours. The residual nitrous gases were released by heating the reaction mixture after diluting it with water.

The solid precipitated product was filtered and washed to give the product **345**. The product obtained showed a new band for C=O at 1700 cm^{-1}, while the band for C=N disappeared. The

product was further confirmed by NMR (ref literature), HRMS and unambiguously confirmed by single crystal X-ray crystallography.

Table 3.9 Hydrolysis of 1,2,4-triazol-3-imine to 1,2,4-triazol-3-one

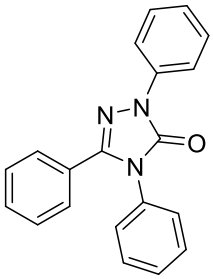


285, **322-323**, **326-328, 333-336**

R_1 = aryl, hetaryl, cylcoalkyl

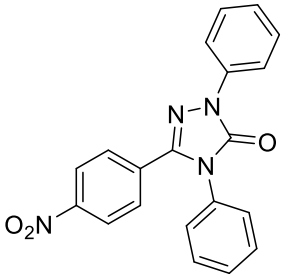
R_2 and R_3 = aryl, H

345-354



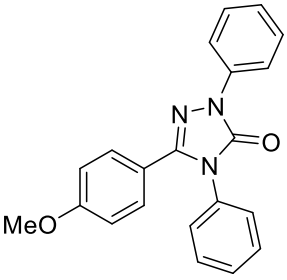
entry 1

345, 76 %



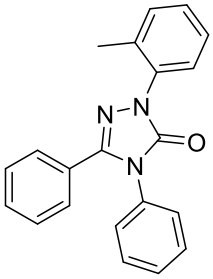
2

346, 89 %



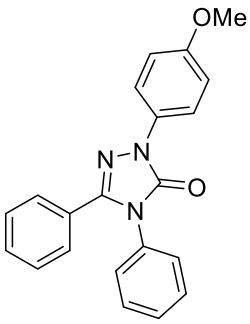
3

347, 84 %



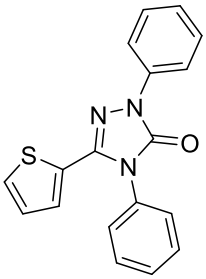
entry 4

349, 80 %



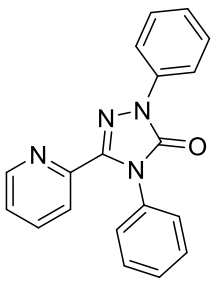
5

350, 82 %



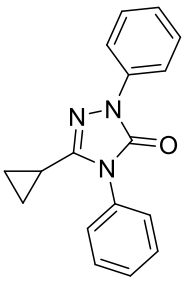
6

351, 73%



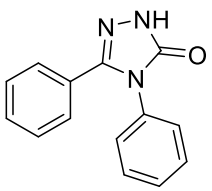
entry 7

352, 88 %



8

353, 79 %



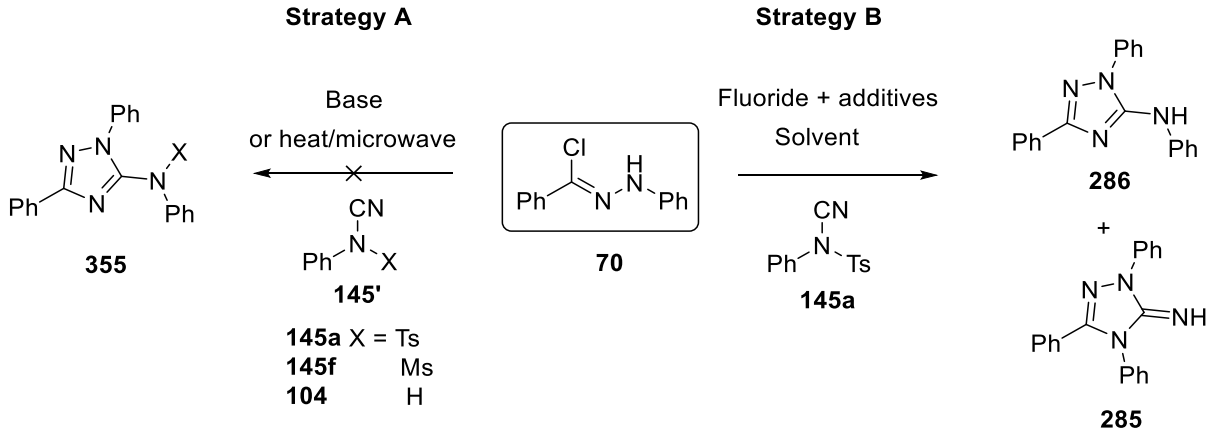
9

354, 73 %

A substrate scope was carried out to test the application of this method towards other 1,2,4-triazol-3-imines bearing aromatic, heteroaromatic, aliphatic and sterically hindered groups, which gave the desired hydrolysis product (**345-354**) in good to excellent yields. The 3,4-diphenyl 1,2,4-triazolone (unsubstituted *N*H) **354** was obtained in a good yield of 70%, showing direct applicability towards ganetespib (**343**) synthesis (Figure 3.11) which shares a similar core as the product **354**.

3.9 Efforts towards preferable formation of 5-anilino-1,2,4-triazole

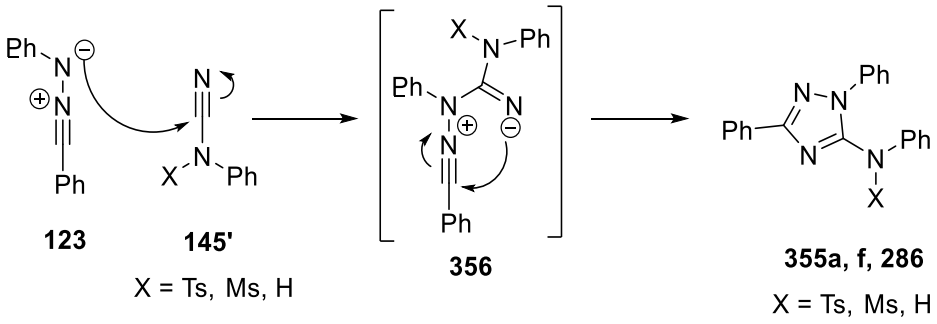
During our preliminary studies on the hydrazonyl chloride with NCTS we observed the competitive formation of the 1,2,4-triazol-3-imine and 5-anilino-1,2,4-triazole in varying ratio (55:45 to 94:6), imine being the major in every case. We optimised the condition for the preferred formation of the 1,2,4-triazol-3-imine over its heterocyclic isomer **286** 5-anilino -1,2,4-triazole in 94:6. Next, efforts were made towards optimising the conditions to access 5-anilino -1,2,4-triazole (**286**) preferably (Scheme 3.13).



Scheme 3.13 Different strategies employed for 5-anilino-1,2,4-triazole synthesis

*Strategy A: Reaction of hydrazonyl chloride **70** with N-substituted cyanamides **145'** in presence of base/heat*

According to strategy **A**, it was hypothesised that introducing a base such as K_2CO_3, Et_3N, *t*-BuOK in the reaction of hydrazonyl chloride **70** and *N*-substituted cyanamide derivatives, would lead to the nitrile imine generation but no cyanamide ion formation. This would facilitate the nucleophilic attack of the nitrile imine on the electrophilic nitrile centre of the cyanamide (**145'**) (Scheme 3.13 and 3.14).



Scheme 3.14 Strategy A: Reaction of **70** and **145'** in presence of base

Based on this hypothesis, reactions were carried out with NCTS (**145a**) in presence of bases like: TEA/DCM/rt, TEA/toluene/microwave (MW)/150 ^{o}C, 1M NaOH/H_2O/Acetone, 5% Na_2CO_3/TBAB/THF/rt, 5% Na_2CO_3/TBAB/THF/MW/150 ^{o}C), *t*-BuOK/THF/50 ^{o}C, *t*-BuOK/toluene/MW/150 ^{o}C, TEA/Cu(I)/toluene/rt, *t*-BuOk/Cu(I)/toluene/rt, and lewis acids like $CuSO_4/H_2O$, $Cu(NO_3)_2/H_2O$, but all the reaction conditions generated nitrile imine (as confirmed by detection of dimer formation-TLC/GC-MS); NCTS remained unconsumed or got degraded (trimer formation). Unfortunately, no anilino-1,2,4-triazole (**355a**) formation was observed.

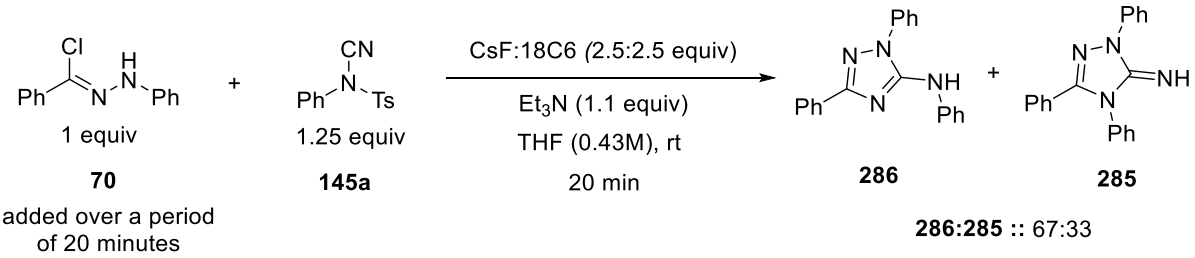
The inability of the nitrile imine to attack the nitrile carbon in NCTS lead us to think if the steric bulk of the toluenesulfonyl group was hindering the reaction. Hence, *N*-methanesulfonyl-*N*-phenyl cyanamide (**145f**, X = Ms) was synthesised and reacted in excess with the hydrazonyl chloride (**70**) under varying conditions – DIPEA/CH_2Cl_2/rt, TEA(excess)/toluene/reflux, neat/132 ^{o}C, neat/µwave/150 ^{o}C. Again, the hydrazonyl chlorides were readily dimerised, with **145f** either getting degraded or remaining unreacted. Thus, even the introduction of a less bulky group (methane sulfonyl) in the cyanamide did not yield the 5-anilino-5-methanesulfonyl-1,2,4-triazole **355f**.

Next, phenyl cyanamide **104 (X = H)**, was reacted with the hydrazonyl chloride under altered conditions - neat/100 ^{o}C, TEA/toluene/reflux which just resulted in the dimer formation and degradation of the phenyl cyanamide. The reaction with DIPEA/DCM/rt resulted in the formation of the dimer and 1,2,4-triazole-5-imine (**285**), instead of the expected 5-anilino 1,2,4-triazole **286**.

*Strategy B: Reaction of hydrazonyl chloride **70** with NCTS **145a** in presence of fluoride source/additives/solvent*

As per our previous study, reactions of hydrazonyl chlorides with NCTS carried out in the presence of fluoride source gave a mixture of 5-anilino-1,2,4-triazole (**286**) and 1,2,4-triazole-3-imine (**285**). Various solvents were screened for the slow addition of hydrazonyl chloride (**70,** 1 hour) to a heterogenous mixture containing **145a**, CsF/18-crown-6 and the ratio of **286**:**285** (amine:imine) were recorded: $CHCl_3$ (16:84), THF (25:75), dioxane (29:71), Et_2O (31:69).

Under the optimised conditions (adding hydrazonyl chloride after 10 minutes), THF was more favourable towards 5-anilino-1,2,4-triazole (**286**) as it returned the products in the ratio of 45:55 (entry 7, Table 3.6). Even more enhancement of the **286**:**285** was observed when 1.1 molar equivalents of TEA was used along with CsF:18-crown-6 (2.5:2.5) in THF, and hydrazonyl chloride (**70**) was added over a period of 20 minutes at room temperature. The above reaction yielded the products in a ratio of 67:33 of **286**: **285**. The ratios were determined by NMR analysis of the crude reaction mixture.



Scheme 3.15 Optimal conditions for preferential formation of 1,2,4-triazol-5-amine (**286**)

3.10 Conclusions and future work

We have demonstrated that 1,2,4-triazole-3-imines (**180**) can be prepared by the cyclisative capture of *in situ* generated nitrile imines (**268**) and cyanamide ion (**199**), using CsF/18-crown-6 as base and fluoride source. The reaction is complete within 20 min, affording a wide variety of 1,2,4-triazol-imine compounds in good to excellent yields.

The 1,2,4-triazol-3-imine core can be further functionalised to pharmaceutically important 1,2,4-triazolone by hydrolysis in good yields. The present methodology offers a new route towards Ganetespib, an investigational anti-cancer drug, the synthesis of which can be a part of future studies.

The selective synthesis of 5-anilino-1,2,4-triazole (**286**) which is the heterocyclic isomer of 1,2,4-triazol-3-imine, can be further investigated. This will further enhance the utility of cyanamide in the construction of different heterocyclic cores.

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Chapter-4

Experimental Section

Chapter 4

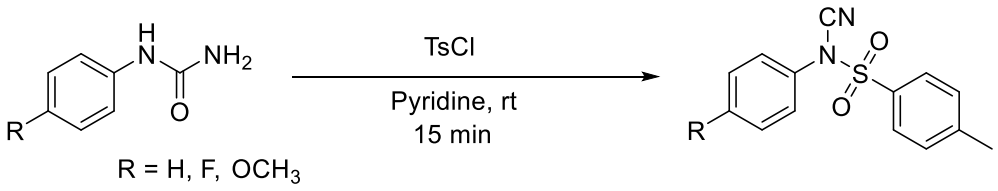
Experimental Section

General Information

^{1}H NMR spectra were recorded on Bruker AV 400, DPX 400 and AV 500 spectrometers at 400 and 500 MHz respectively. ^{13}C NMR spectra were recorded using the same spectrometers at 100 and 125 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.27, δ_C at 77.00 ppm, MeOD at δ_H 3.31, δ_C at 49.15 ppm). *J* values are given in Hz and s, d, dd, t, td, q, m and br abbreviations correspond to singlet, doublet, doublet of doublet, triplet, triplet of doublet, quartet, multiplet, broad and combinations thereof. High-resolution mass spectra (HRMS) were recorded on a VG micron Autospec or Bruker microTOF. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory or Bruker Alpha FT-IR Spectrometer, deposited neat to a diamond/ZnSe plate. Specific rotation of the samples were measured using polarimeter in concentration of 1g/100 ml, path length – 0.5 dm^3 and temperature – 24.5^{o} C. An average of 5 readings was taken. Melting Point was recorded on a Stuart SMP10 digital melting point apparatus.

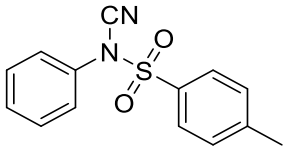
Column chromatography was carried out using silica gel 60 and thin layer chromatography was performed using silica gel 60 F254 pre-coated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$, alcoholic solution of *p*-anisaldehyde, or molecular iodine as appropriate. Petroleum ether refers to petroleum ether (40–60 %) and EtOAc refers to ethyl acetate. Conc. HCl refers to the 37 % HCl analytical grade. NH_3 refers to 37% aqueous solution of ammonia. All chemicals were used without further purification unless otherwise stated.

4.1 General Procedure for the synthesis of *N*-aryl *N*-toluenesulfonyl cyanamide[1]



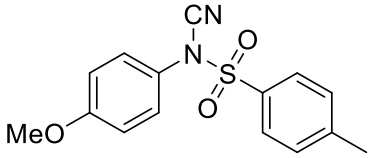
A 250 mL round bottom flask was charged with aryl urea (8 mmol) and dissolved by addition of pyridine (54 mL). The flask was immersed in room temperature water bath. *p*-toluenesulfonyl chloride (27.7 mmol) was added portion wise over 3 min. The reaction mixture was stirred for additional 15 min and poured into ice-cold water (400 mL) with mechanical stirring. Precipitate formed during mechanical stirring was filtered under vacuum and washed with water. Precipitated product was further purified by column chromatography using Pet ether:EtOAC (9:1) as eluent to yield *N*-aryl *N*-tosyl cyanamide.

***N*-phenyl *N*-toluenesulfonyl cyanamide (145a)**[2]



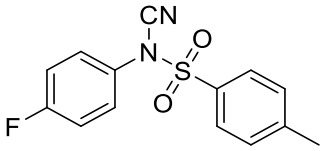
Following general procedure 4.1: *N*-Phenyl urea (1.08 g, 8 mmol) and *p*-toluenesulfonyl chloride (5.27 g, 27.7 mmol) were reacted to afford the product **145a** (1.62 g, 74 % yield) as a white crystalline solid; M. p. 85-87 °C (85-87 °C)[1]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.45 – 7.34 (m, 5H, Ar-H), 7.21-7.19 (m, 2H, Ar-H), 2.48 (s, 3H, CH_3) ppm;^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7 (C), 134.5 (C), 132.3 (C), 130.2 (CH), 129.9 (CH), 129.8 (CH), 128.4 (CH), 126.4 (CH), 108.6 (C), 21.8 (CH_3) ppm; IR: ῡ (cm^{-1}) 2232, 1591, 1485, 1389, 1171.

***N*-(4-Methoxyphenyl) *N*-toluenesulfonyl cyanamide (145b)**



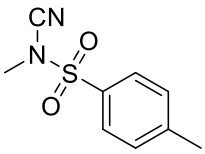
Following general procedure 4.1: 4-methoxyphenyl urea (0.5 g, 3.0 mmol) and *p*-toluenesulfonyl chloride (1.98 g, 10.4 mmol) were reacted to afford the product **145a** (0.47 g, 52 % yield) as a white crystalline solid; M. p. 117-118 °C; R_f 0.55 (4:1 Pet Ether:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.61 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.34 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.05 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.84 (d, *J* = 9.0 Hz, 2H, Ar-H), 3.8 (s, 3H, O$C\underline{H}_3$), 2.47 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) : *δ* 160.6 (C), 146.6 (C), 132.0 (C), 130.1 (CH), 128.3 (CH), 128.2 (CH), 126.6 (C), 114.8 (CH), 108.7 (C), 55.5 (OCH_3), 21.7 (CH_3); IR: ῡ (cm^{-1}): 2923, 2848, 2230, 1589, 1503, 1399, 1174 ; HRMS (ESI) calculated for $C_{15}H_{15}N_2O_3S$ $[M+H]^+$ 303.0798, found: 303.0796.

***N*-(4-Fluorophenyl) *N*-toluenesulfonyl cyanamide (145c)**



Following general procedure 4.1: 4-fluorophenyl urea (0.5 g, 3.25 mmol) and *p*-toluenesulfonyl chloride (2.14 g, 11.2 mmol) were reacted to afford the product **145a** (0.24 g, 26 % yield) as a white crystalline solid; M. p. 108-109 °C; R_f 0.63 (4:1 Pet Ether:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.4 Hz, 2H, Ar-H), 7.36 (d, J = 8.4 Hz, 2H, Ar-H), 7.18-7.15 (m, 2H, Ar-H), 7.09-7.04 (m, 2H, Ar-H), 2.48 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 162.9 (C, d, J = 250.6 Hz), 146.9 (C), 131.8 (C), 130.3 (CH), 128.6 (CH, d, J = 9.1 Hz), 128.3 (CH), 116.8 (CH, d, J = 23.3 Hz), 108.4 (C), 21.7 (CH_3); IR: $\tilde{\upsilon}$ (cm^{-1}) 2232, 1595, 1498, 1386, 1179; HRMS (ESI) calculated for $C_{14}H_{12}FN_2O_2S$ $[M+H]^+$ 291.0598, found: 291.0593.

***N*-methyl *N*-toluenesulfonyl cyanamide (145d)**



Following general procedure 4.1: *N*-methyl urea (1.0 g, 13.5 mmol) and *p*-toluenesulfonyl chloride (8.9 g, 46.7 mmol) were reacted to afford the product **145a** (2.0 g, 72 % yield) as a white crystalline solid; M. p. 67-68 °C; R_f 0.32 (4:1 Pet Ether:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.3 Hz, 2H, Ar-H), 7.44 (d, J = 8.0 Hz, 2H, Ar-H), 3.14 (s, 3H, *N*-C$\underline{H}_3$), 2.50 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) : 146.6 (C), 132.5 (C), 130.5 (CH), 127.9 (CH), 109.4 (C), 36.8 (*N*–CH_3), 21.7 (CH_3) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 2232, 1595, 1498, 1385, 1177; HRMS (ESI) calculated for $C_9H_{11}N_2O_2S$ $[M+H]^+$ 211.0462, found: 211.0474.

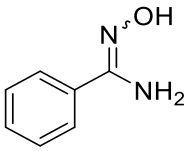
4.2 Synthesis of *N*-aryl and *N*-alkyl cyanamides

4.2.1 General procedure for the preparation of amidoximes from carbonitriles [3]

To the solution of carbonitrile in EtOH (0.1 M) was added 50*wt*% aqueous hydroxylamine solution (1.5~2 equiv). The mixture was stirred at reflux temperature for 3 h under nitrogen.

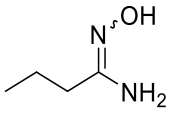
After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue was used for the subsequent reaction without further purification.

Benzamidoxime (219):[4]



Compound **219** was prepared by the *Procedure 4.2.1* from benzonitrile (5.0 g, 48.5 mmol) **218**. The crude product was used for the subsequent reaction without further purification (white solid, 5.34 g, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H, OH), 7.71-7.69 (m, 2H, Ar-H), 7.38-7.36 (m, 3H, Ar-H), 5.82 (s, 2H, N*H*$_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0 (C), 133.4 (CH), 129.0 (CH), 128.2 (CH), 125.5 (C).

Butyramidoxime (251)[4]:



Compound **251** was prepared by the *Procedure 4.2.1* from propionitrile (3.0 g, 43.4 mmol) **250**. The crude product was used for the subsequent reaction without further purification (colourless oil, 3.37 g, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (br s, 1 H, O*H*), 4.63 (s, 2 H, N*H*$_2$), 2.10 (t, *J* = 7.4 Hz, 2 H, C*H*$_2$), 1.61-1.51 (m, 2 H, C*H*$_2$), 0.93 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9 (C), 33.0 (CH_2), 20.0 (CH_2), 13.4 (CH_3).

4.2.2 General procedure for the preparation of N-substituted cyanamides from amidoximes with p-toluenesulfonyl chloride[4]

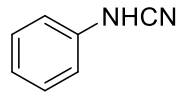
To the mixture of amidoxime and DIPEA (1.05 equiv) in CH_2Cl_2 (0.1 M) at 0 °C was added *p*-TsCl (1.05 equiv). The mixture was stirred for 3 h under nitrogen while the temperature was allowed to rise to room temperature. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography.

4.2.3 General procedure for the preparation of N-substituted cyanamides from amidoximes with o-nitrobenzenesulfonyl chloride[4]

To the mixture of amidoxime and DIPEA (1.05 equiv) in CH_2Cl_2 (0.1 M) at 0 °C was added *o*-NsCl (1.05 eq). The mixture was stirred at 0 °C for 10 min and then at reflux temperature for 1

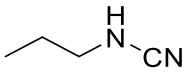
hour under nitrogen. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography.

***N*-Phenylcyanamide[4] (104)**:



The compound (**104**) was prepared by the *Procedure 4.2.2* from benzamidoxime (3.0 g, 22.0 mmol) and *p*-toluene sulfonyl chloride (4.4 g, 23.1 mmol) **219**. The reaction was purified by column chromatography (Pet. Ether / EtOAc = 8 : 2, R_f = 0.20) to give **38a** (brown syrup, 1.95 g, 75% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.08 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.02 (d, *J* =8.5 Hz, 2 H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3 (C), 129.6 (CH), 123.4 (CH), 115.3 (CH), 111.8 (C); IR: ῡ cm^{-1} :3461, 3173, 2982, 2915, 2221, 1594.

***N*-propyl cyanamide[4] (252)**:



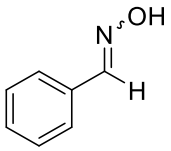
The compound (**252**) was prepared by the *Procedure 4.2.2* from butyramidoxime **251** (2.0 g, 19.6 mmol) and *o*-nitro phenylsulfonyl chloride (4.55 g, 20.5 mmol). The reaction was purified by column chromatography (Pet. Ether / EtOAc = 8 : 2, R_f = 0.35) to give **252 (**Yellow oil, 1.05 g, 64 % yield), ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 4.48 (s, 1H, N*H*), 3.00-2.96 (m, 2H, CH_2), 1.63-1.54 (m, 2H, CH_2), 0.93 (t, *J* = 7.5 Hz, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *δ* = 116.8 (CN), 47.5 (CH_2), 22.8 (CH_2), 10.6 (CH_3) ppm; IR: ῡ cm^{-1}= 2970, 2676, 2214, 1538, 1464.

4.3 Synthesis of oximes and hydroximoyl chlorides

*4.3.1 General procedure for the preparation of aldoximes (**210**) from aldehydes (**209**)*[5]

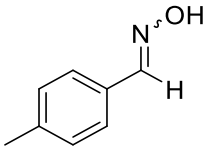
A mixture of the aldehyde (20.0 mmol), hydroxylamine hydrochloride (26 mmol) and Na_2CO_3 (4.6 mmol) in 60 ml of water was refluxed for 2 h. After the reaction mixture was allowed to cool down to room temperature, it was extracted with dichloromethane (2 × 40 ml), and the organic fractions were combined and concentrated under reduced pressure. The residue was used for the subsequent reaction without further purification.

Benzaldehyde oxime[6] (210a)



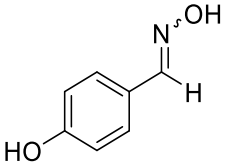
Following general procedure 4.3.1: Benzaldehyde (2.12 g, 20 mmol) gave the product **210a** (2.4 g, 99 % yield) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H, sp^2 CH), 7.65-7.57 (m, 3H, OH and Ar-H), 7.42-7.38 (m, 3H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3 (C), 131.8 (C), 129.9 (CH), 128.6 (CH), 126.9 (CH) ppm.

4-methyl benzaldehyde oxime[6] (210b)



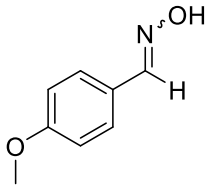
Following general procedure 4.3.1: 4-methylbenzaldehyde (2.4 g, 20 mmol) gave the product **210a** (2.64 g, 98 % yield) as a white solid; M. p. 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.78 (brs, 1H, OH), 8.16 (s, 1H, sp^2 CH), 7.49 (d, J = 8.1 Hz, 2H, Ar-H), 7.21 (d, J = 8.1 Hz, 2H, Ar-H), 2.39 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 150.3 (CH), 140.3 (C), 129.5 (CH), 129.1 (C), 126.9 (CH), 21.4 (CH_3) ppm.

4-hydroxy benzaldehyde oxime[6] (210c)



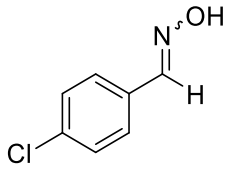
Following general procedure 4.3.1: 4-hydroxybenzaldehyde (2.45 g, 20 mmol) gave the product **210a** (2.6 g, 95 % yield) as a brown solid; M. p. 75-77 °C; ^{1}H NMR (400 MHz, MeOD): 7.99 (s, 1H, sp^2 CH), 7.41 (d, J = 8.2 Hz, 2H, Ar-H), 6.78 (d, J = 8.5 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, MeOD): δ 160.1 (C), 150.5 (C), 134.1 (CH), 129.4 (C), 125.6 (C), 116.6 (CH) ppm.

4-methoxy benzaldehyde oxime[6] (210d)



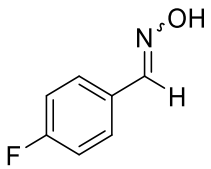
Following general procedure 4.3.1: 4-methoxybenzaldehyde (2.7 g, 20 mmol) gave the product **210a** (2.87 g, 96 % yield) as a yellow solid; M. p. 51-54 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.14 (s, 1H, sp^2 CH), 7.54 (d, J = 8.78 Hz, 2H, Ar-H), 6.92 (d, J = 8.78 Hz, 2H, Ar-H), 3.83 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 161.0 (C), 149.9 (CH), 128.5 (CH), 124.5 (C), 114.2 (CH), 55.2 (CH_3) ppm

4-chloro benzaldehyde oxime[6] (210e)



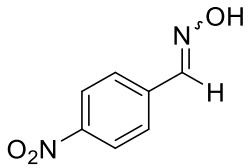
Following general procedure 4.3.1: 4-chlorobenzaldehyde (2.8 g, 20 mmol) gave the product **210a** (2.97 g, 96 % yield) as a white solid; M. p. 108-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.73 (brs, 1H, OH), 8.14 (s, 1H, sp^2 CH), 7.54-7.50 (m, 2H, Ar-H), 7.39-7.36 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 149.3 (CH), 136.0 (C), 130.3 (C), 129.0 (CH), 128.2 (CH) ppm.

4-fluoro benzaldehyde oxime (210f)



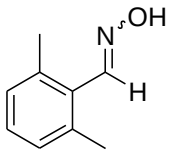
Following general procedure 4.3.1: 4-fluorobenzaldehyde (2.5 g, 20 mmol) gave the product **210a** (2.6 g, 93 % yield) as a white solid; M. p. 85-87 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.74 (brs, 1H, OH), 8.15 (s, 1H, sp^2 CH), 7.60-7.55 (m, 2H, Ar-H), 7.13-7.06 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 163.7 (C, d, J = 260.6 Hz), 149.3 (CH), 128.8 (CH, d, J = 8.4 Hz), 128.1 (C, d, J = 3.0 Hz), 115.9 (CH, d, J = 22.2 Hz) ppm.

4-nitro benzaldehyde oxime[6] (210g)



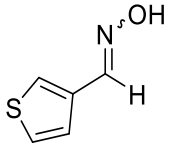
Following general procedure 4.3.1: 4-nitrobenzaldehyde (3.0 g, 20 mmol) gave the product **210a** (3.2 g, 97 % yield) as a yellow solid; M. p. 129-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.26 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.22 (s, 1H, sp^2 CH), 8.07 (brs, 1H, OH), 7.76 (d, *J* = 8.9 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 148.3 (CH), 138.1 (C), 127.6 (CH), 124.0 (CH), 123.7 (C) ppm.

2,6-dimethylbenzaldehyde oxime (210h)



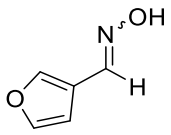
Following general procedure 4.3.1: 2,6-dimethylbenzaldehyde (2.7 g, 20 mmol) gave the product **210a** (2.9 g, 97 % yield) as a white solid; M. p. 151-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.92 (brs, 1H, OH), 8.47 (s, 1H, sp^2 CH), 7.22-7.19 (m, 1H, Ar-H); 7.11 Hz (d, *J* = 7.53Hz, 2H, Ar-H), 2.45 (s, 6H, 2 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) : δ 149.7 (CH), 137.4 (C), 129.3 (C), 128.9 (CH), 128.4 (CH), 20.9 (CH_3) ppm.

Thiophene-3-carbaldehyde oxime[6] (210i)



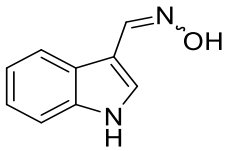
Following general procedure 4.3.1: 3-thiophene carboxaldehyde (2.2 g, 20 mmol) gave the product **210a** (2.4 g, 98 % yield) as a brown solid; mixture of *E* and *Z* isomer (57:43 mixture); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (br s, 1H), 8.24 (s, 1H, major), 8.21 (dd, *J* = 3.0; 1.1 Hz, 1H, minor), 7.53-7.52 (m, 1H, major), 7.50 (dd, *J* = 3.0; 1.2 Hz, 1H, major), 7.44 (*app* d, *J* = 0.9 Hz, 1H, minor), 7.43 (d, *J* = 1.2 Hz, 1H, major), 7.35-7.32 (m, 1H, minor), 7.34 (m, 1H, major). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6 (CH), 141.0 (CH), 134.1 (C), 131.4 (CH), 131.2 (C), 129.3 (CH), 126.8 (CH), 125.1 (CH), 124.7 (CH) ppm.

Furan-3-carbaldehyde oxime (210j)



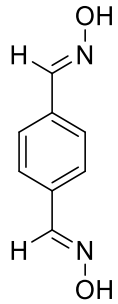
Following general procedure 4.3.1: 3-furan carboxaldehyde (1.9 g, 20 mmol) gave the product **210a** (2.2 g, 99 % yield) as a brown solid; mixture of *E* and *Z* isomer (1:1 mixture); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.10 (brs, 2H, OH), 8.27 (br s, 1H, *E*-isomer), 8.12 (s, 1H, *Z*-isomer), 7.66 (brs, 1H, *Z*-isomer), 7.45 (t, *J* = 1.7 Hz, *E*-isomer), 7.43 (m, 1H, *Z*-isomer), 7.39 (brs, 1H, *E*-isomer), 6.75 (m, 1H, *Z*-isomer), 6.68 (dd, *J* = 1.2; 0.5 Hz, 1H, *E*-isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1 (CH, *E*-isomer), 144.1 (CH, *Z*-isomer), 143.7 (CH, *Z*-isomer), 142.7 (CH, *E*-isomer), 142.6 (CH, *Z*-isomer), 139.7 (CH, *E*-isomer), 119.4 (C, *Z*-isomer), 116.0 (C, *E*-isomer), 110.7 (CH, *E*-isomer), 107.2 (CH, *Z*-isomer) ppm.

Indole-3-carbaldehyde oxime (210k)



Following general procedure 4.3.1: 3-Indole caboxaldehyde (2.9 g, 20 mmol) gave the product **210a** (3.0 g, 94 % yield) as a white solid; M. p. 172-173 °C (lit- 196-198 °C); ^{1}H NMR (400 MHz, $CDCl_3$): 8.31-8.29 (m, 1H), 7.75-7.70 (m, 2H), 7.40-7.38 (m, 1H), 7.19-7.11 (m, 2H) ppm, ESI M^+ (m/z) for $C_9H_8N_2O$ – 160.0732

Terepthaldehyde dioxime[7] (210l)

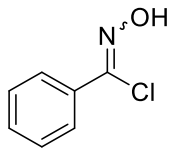


Following general procedure 4.3.1: Terepthaldehyde (2.7 g, 20 mmol) gave the product **210a** (3.2 g, 98 % yield) as a white solid; M. p. 184-185 °C; ^{1}H NMR (400 MHz, MeOD): 8.15 (s, 2H, sp^2 CH), 7.66 (s, 4H, Ar-H); ^{13}C NMR (100 MHz, MeOD): *δ* 149.7 (CH), 135.6 (C), 128.1 (CH) ppm.

*4.3.2 General procedure for the preparation of hydroximoyl chlorides (**211**) from aldoximes (**210**)*[8]

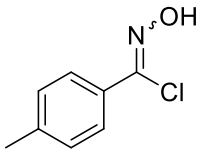
To a solution of 10 mmol of oxime in DMF (10 mL) was added 1.8 mmol of *N*-chlorosuccinimide (NCS) in one portion. (The beginning of the reaction can be detected by a slight increase of the reaction temperature. If the reaction does not start, heat was applied with a heat-gun to initiate the reaction. With the electron-deficient oximes, the reaction mixture was heated to 45 °C.) The remaining 8.2 mmol of NCS was added in small portions while keeping the temperature below 35 °C (below 60 °C for electron-deficient oximes). The mixture was stirred at room temperature for 1 h, poured into water, and extracted with dichloromethane. The organic phase was washed with brine and dried over Na_2SO_4, and the solvent was removed to give the imidoyl chloride products in 50-90% yield after column chromatography.

_N_-hydroxybenzimidoyl chloride (211a)



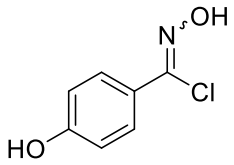
Following general procedure 4.3.2: Benzaldehyde oxime (1.2 g, 10 mmol) gave the product **211a** (1.32 g, 86 % yield) as a white solid; M. p. 48-49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (brs, 1H, OH), 7.88-7.84 (m, 2H, Ar-*H*), 7.49-7.40 (m, 3H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5 (C), 132.3 (C), 130.8 (CH), 128.5 (CH), 127.1 (CH) ppm; HRMS (ESI) calculated for $[M+H]^+$ 156.0211, C_7H_7ClNO found: 156.0219.

_N_-hydroxy 4-methylbenzimidoyl chloride (211b)



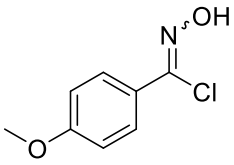
Following general procedure 4.3.2: 4-methylbenzaldehyde oxime (1.35 g, 10 mmol) gave the product **211a** (1.15 g, 68 % yield) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H, OH), 7.76 (d, J = 8.28 Hz, 2H, Ar-H); 7.25 (d, J = 8.03 Hz, 2H, Ar-H), 2.43 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2 (C), 140.5 (C), 129.5 (C), 129.2 (CH), 127.1 (CH), 21.3 (CH_3) ppm.

***N*, 4-dihydroxybenzimidoyl chloride (211c)**



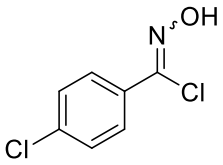
Following general procedure 4.3.2: 4-hydroxybenzaldehyde oxime (1.37 g, 10 mmol) gave the product **211a** (0.87 g, 51 % yield) as a brown syrup; ^{1}H NMR (400 MHz, MeOD) 7.67-7.64 (m, 2H, Ar-H), 7.25 Hz (d, *J* = 8.03 Hz, 2H, Ar-H), 2.43 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, MeOD): δ 160.4 (C), 138.5 (C), 129.6 (CH), 125.7 (C), 116.1 (CH) ppm.

***N*-hydroxy-4-methoxybenzimidoyl chloride (211d)**



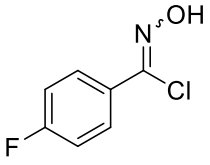
Following general procedure 4.3.2: 4-methoxybenzaldehyde oxime (1.51 g, 10 mmol) gave the product **211a** (1.55 g, 84 % yield) as a yellow solid; M. p. 84-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.82 (s, 1H, OH), 7.78 (d, *J* = 9.0 Hz, 2H, Ar-H); 6.93 (d, *J* = 9.0 Hz, 2H, Ar-H), 3.85 (s, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5 (C), 140.0 (C), 128.7 (CH), 124.8 (C), 113.8 (CH), 55.4 (CH_3) ppm.

4-chloro-*N*-hydroxybenzimidoyl chloride (211e)



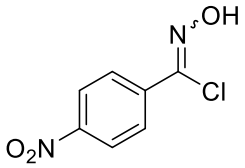
Following general procedure 4.3.2: 4-chlorobenzaldehyde oxime (1.55 g, 10 mmol) gave the product **211a** (1.29 g, 68 % yield) as a white solid; M. p. 88-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.85 (s, 1H, OH), 7.76 (d, *J* = 8.9 Hz, 2H, Ar-H); 7.38 (d, *J* = 8.9 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6 (C), 137.0 (C), 130.7 (C), 128.7 (CH), 128.3 (CH) ppm.

4-fluoro-*N*-hydroxybenzimidoyl chloride (211f)



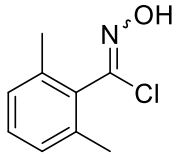
Following general procedure 4.3.2: 4-fluorobenzaldehyde oxime (1.4 g, 10 mmol) gave the product **211a** (1.36 g, 79 % yield) as a white solid; M. p. 70-72°C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.85-7.81 (m, 2H, Ar-H); 7.14-7.08 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2 (C, d, J = 251.7 Hz), 139.6 (C), 129.2 (CH, d, J = 8.78 Hz), 128.4 (C, d, J = 2.93 Hz), 115.6 (CH, d, J = 21.96 Hz) ppm

4-nitro-*N*-hydroxybenzimidoyl chloride (211g)



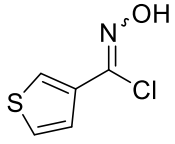
Following general procedure 4.3.2: 4-nitrobenzaldehyde oxime (1.66 g, 10 mmol) gave the product **211a** (1.44 g, 72 % yield) as a yellow solid; M. p. 123-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.28 (d, J = 9.16 Hz, 2H, Ar-H), 8.19 (s, 1H, OH), 8.05 (d, J = 9.16 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9 (C), 138.1 (C), 133.1 (C), 128.0 (CH), 123.7 (CH) ppm.

***N*-hydroxy-2,6-dimethylbenzimidoyl chloride (211h)**



Following general procedure 4.3.2: 2,6-dimethylbenzaldehyde oxime (1.5 g, 10 mmol) gave the product **211a** (0.95 g, 52 % yield) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): 8.28 (d, J = 9.16 Hz, 2H, Ar-H), 8.19 (s, 1H, OH), 8.05 (d, J = 9.16 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9 (C), 138.1 (C), 133.1 (C), 128.0 (CH), 123.7 (CH) ppm.

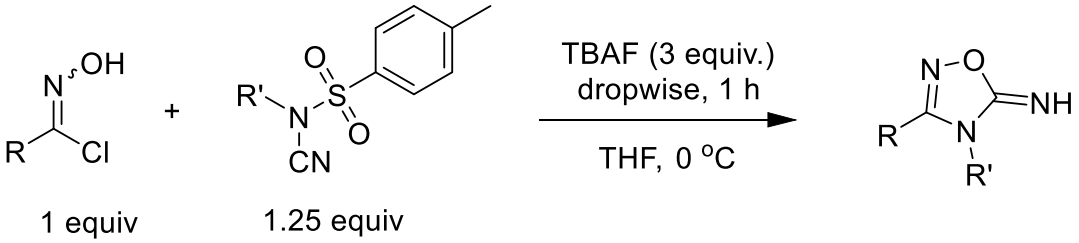
***N*-hydroxythiophene-3-carbimidoyl chloride (211i)**



Following general procedure 4.3.2: thiophene carbaldehyde oxime (1.27 g, 10 mmol) gave the product **211a** (1.4 g, 87 % yield) as a yellow solid; mixture of isomers (57:43); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79-7.78 (m, 1H, major), 7.43 (d, J = 5.0 Hz, 1H, minor), 7.33 (*m*, 1H, major), 7.10 (d, J = 5.5 Hz, 1H, major); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0 (C), 134.4 (C), 131.6 (C), 127.3 (CH) 126.6 (CH), 125.2 (CH), 124.2 (CH), 123.9 (CH) ppm

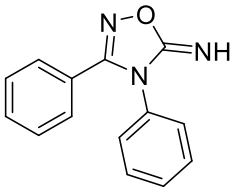
4.4 Synthesis of 1,2,4-oxadiazol-5(4*H*)-imine

4.4 General procedure for the synthesis of 1,2,4 –oxadiazol-5(4H)-imine



Hydroximoyl chloride (1 equiv., 0.64 mmol) and *N*-aryl-*N*-tosyl cyanamide (1.25 equiv., 0.80 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar. The substrates were dissolved in anhydrous THF (0.5 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 °C (ice-bath) and TBAF (1M in THF, 3 equiv., 1.92 mmol, 1.92 mL) was added through a syringe pump at the rate of 1.92 mL/hour. After the addition, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 10 mL ethyl acetate, and washed with water (2 x 5 mL) and brine (1 x 5 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure and purified by column chromatography.

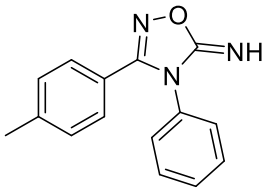
3,4-Diphenyl-1,2,4-oxadiazol-5(4*H*)-imine (214)



N-Hydroxybenzimidoyl chloride **6a** (100 mg, 0.64 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (218 mg, 0.80 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar under argon. The substrates were dissolved in anhydrous THF (0.5 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 °C (ice-bath) and TBAF (1M in THF, 1.92 mL, 1.92 mmol) was added through a syringe pump at the rate of 1.92 mL/hour. After the addition, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 10 mL ethyl acetate, and washed with water (2 x 5 mL) and brine (1 x 5 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced

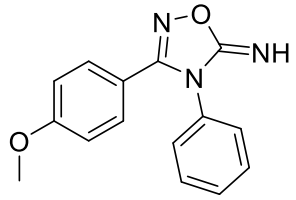
pressure and purified by column chromatography on silica gel using Pet Ether: EtOAc (9:1 to 7:3) to afford the product **1a** (120 mg, 79% yield) as a white solid, 79% yield; M. p. 146-147 °C; R_f 0.35 (1:1 Pet Ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.32 (m, 4H, Ar-H), 7.30-7.24 (m, 4H, Ar-H), 7.20-7.19 (m, 1H, Ar-H), 7.18-7.15 (m, 1H, Ar-H), 5.54 (brs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) : δ 160.8 (C), 157.2 (C), 133.3 (C), 131.6 (CH), 129.9 (CH), 129.2 (CH), 128.8 (CH), 128.3 (CH), 127.5 (CH), 123.2 (C),; IR: ϑ (cm^{-1}) 3288, 1692, 1589, 1498; HRMS (ESI) calculated for $C_{14}H_{12}N_3O$ $[M+H]^+$ 238.0975, found: 238.0982.

4-Phenyl-3-(*p*-tolyl)-1,2,4-oxadiazol-5(4*H*)-imine (220)



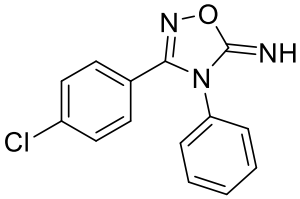
N-Hydroxy 4-methylbenzimidoyl chloride **6b** (100 mg, 0.59 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (200 mg, 0.73 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar under argon. The substrates were dissolved in anhydrous THF (0.5 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 oC (icebath) and TBAF (1M in THF, 1.77 mL, 1.77 mmol) was added through a syringe pump at the rate of 1.77 mL/hour. After the addition, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 10 mL ethyl acetate, and washed with water (2 x 5 mL) and brine (1 x 5 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure and purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1 to 7:3) to afford the product **1b** (111 mg, 75% yield) as a white solid, 75% yield; M. p. 165-166 °C; R_f 0.35 (1:1 Pet Ether:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.42 (m, 3H, Ar-H), 7.30-7.23 (m, 4H, Ar-H), 7.16-7.14 (m, 2H, Ar-H), 2.36 (s, 3H, C$\underline{H}_3$) ppm ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ 160.8 (C), 157.1 (C), 142.0 (C), 133.3 (C), 129.8 (CH), 129.4 (CH), 129.1 (CH), 128.1 (CH), 127.5 (CH), 120.1 (C), 21.4 (CH_3) ppm; IR: ϑ (cm^{-1}) 3177, 1678, 1584, 1430; HRMS (ESI) calculated for $C_{15}H_{14}N_3O$ $[M+H]^+$ 252.1131, found: 252.1119.

3-(4-Methoxyphenyl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-imine (219)



Following general procedure 4.4: *N*-Hydroxy-4-methoxybenzimidoyl chloride **6c** (100 mg, 0.54 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (183 mg, 0.67 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar under argon. The substrates were dissolved in anhydrous THF (0.5 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 °C (icebath) and TBAF (1M in THF, 1.61 mL, 1.61 mmol) was added through a syringe pump at the rate of 1.61 mL/hour. After the addition, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 20 mL ethyl acetate, and washed with water (2 x 5 mL) and brine (1 x 5 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel using Pet Ether:EtOAc (8:2 to 2:8) to afford the product **1c** (121 mg, 84% yield) as a white solid, 84% yield; M. p. 131-133 °C R_f 0.28 (1:1 Pet Ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.44 (m, 3H, Ar-H), 7.27-7.25 (m, 4H, Ar-H), 6.83-6.81 (m, 2H, Ar-H), 5.59 (brs, 1H, N*H*), 3.79 (s, 3H, OC*H*$_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) : δ 161.9 (C), 160.8 (C), 156.8 (C), 133.4 (C), 129.8 (CH), 127.6 (CH), 115.1 (C), 114.2 (CH), 55.3 (OCH_3) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3296, 2852, 1675, 1606, 1586; HRMS (ESI) calculated for $C_{15}H_{14}N_3O_2$ $[M+H]^+$ 268.1081, found: 268.1091.

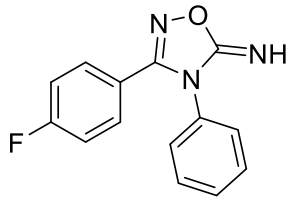
3-(4-Chlorophenyl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-*imine* (223)



Following general procedure 4.4: 4-Chloro-*N*-hydroxybenzimidoyl chloride **6d** (100 mg, 0.52 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (179 mg, 0.65 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar under argon. The substrates were dissolved in anhydrous THF (0.5 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 °C (icebath) and TBAF (1M in THF, 1.60 mL, 1.60 mmol) was added through a syringe pump at the rate of 1.60 mL/hour. After the addition, the flask

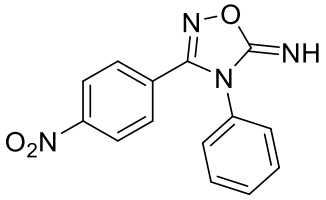
was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 10 mL ethyl acetate, and washed with water (2 x 5 mL) and brine (1 x 5 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure and purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1 to 6:4) to afford the product **1d** (95 mg, 67% yield) as a white solid, 67% yield; M. p. 153-155 °C; R_f 0.41 (1:1 Pet Ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.20-6.18 (m, 3H, Ar-H), 6.06-5.98 (m, 6H, Ar-H), 4.35 (brs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) : δ 160.4 (C), 156.2 (C), 137.8 (C), 132.9 (C), 129.9 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 127.4 (CH), 121.5 (C) ppm; IR: ῡ (cm^{-1}) 3170, 2922, 2852, 1679, 1581; HRMS (ESI) calculated for $C_{14}H_{11}ClN_3O$ $[M+H]^+$ 272.0585, found: 272.0580.

3-(4-Fluorophenyl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-imine (222)



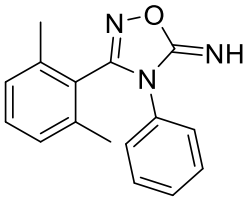
Following general procedure 4.4: 4-Fluoro-*N*-hydroxybenzimidoyl chloride **6e** (100 mg, 0.57 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (196 mg, 0.72 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar under argon. The substrates were dissolved in anhydrous THF (0.5 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 °C (icebath) and TBAF (1M in THF, 1.75 mL, 1.75 mmol) was added through a syringe pump at the rate of 1.75 mL/hour. After the addition, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 10 mL ethyl acetate, and washed with water (2 x 5 mL) and brine (1 x 5 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure and purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1 to 7:3) to afford the product 1e (92 mg, 63% yield) as a white solid, 63% yield; M. p. 127-131 °C; R_f 0.38 (1:1 Pet Ether:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.31 (m, 3H, Ar-H), 7.27-7.23 (m, 2H, Ar-H), 7.18-7.15 (m, 2H, Ar-H), 6.95-6.90 (m, 2H, Ar-H), 5.47 (s, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) : δ 164.2 (C, d, J = 253 Hz), 160.5 (C), 156.1 (C), 132.9 (C), 130.3 (CH, d, J = 8.7 Hz), 129.8 (CH), 129.3 (CH), 127.4 (CH), 119.1 (C, d, J = 3.3 Hz), 116.0 (CH, d, J = 22.3 Hz) ppm; IR: ῡ (cm^{-1}) 3286, 1691, 1433; HRMS (ESI) calculated for $C_{14}H_{11}FN_3O$ $[M+H]^+$ 256.0881, found: 256.0895.

3-(4-Nitrophenyl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-imine (224)



Following general procedure 4.4: 4-Nitro-*N*-hydroxybenzimidoyl chloride **6f** (100 mg, 0.50 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (169 mg, 0.62 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar under argon. The substrates were dissolved in anhydrous THF (0.5 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 °C (icebath) and TBAF (1M in THF, 1.5 mL, 1.5 mmol) was added through a syringe pump at the rate of 1.5 mL/hour. After the addition, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 30 mL ethyl acetate, and washed with water (2 x 10 mL). The aqueous fractions were re-extracted with ethyl acetate (2 x 10 mL), and the organic fractions were combined and washed with brine (1 x 5 mL). The organic fractions were then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue obtained was purified by column chromatography on silica gel using Pet Ether:EtOAc (8:2 to 2:8) to afford the product **1f** (49 mg, 35% yield) as a brown solid, 35% yield; M. p. 148-149 °C; R_f 0.30 (1:1 Pet Ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32-8.15 (m, 3H, Ar-H), 7.59-7.49 (m, 6H, Ar-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) : δ 155.7 (C), 155.4 (C), 149.4 (C), 132.6 (C), 131.3 (C), 130.2 (CH), 130.1 (CH), 129.8 (CH), 129.2 (CH), 129.2 (CH), 127.3 (CH), 126.7 (CH), 124.1 (CH), 123.9 (CH) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3315, 1681, 1537, 1433; HRMS (ESI) calculated for $C_{14}H_{11}N_4O_3$ $[M+H]^+$ 283.0826, found: 283.0821.

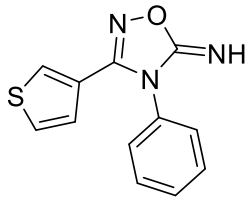
3-(2, 6-Dimethylphenyl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-imine (221)



Following general procedure 4.4: *N*-Hydroxy-2,6-dimethylbenzimidoyl chloride **6g** (100 mg, 0.54 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (185 mg, 0.68 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar under argon. The substrates were dissolved in anhydrous THF (0.5 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 °C (icebath) and TBAF (1M in THF, 1.60 mL, 1.60 mmol)

was added through a syringe pump at the rate of 1.60 mL/hour. After the addition, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 10 mL ethyl acetate, and washed with water (2 x 5 mL) and brine (1 x 5 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure and purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1 to 1:1) to afford the product **1g** (105 mg, 73% yield) as a white solid, 73% yield; M. p. 128-132 °C; R_f 0.51 (1:1 Pet Ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.20 (m, 4H, Ar-H), 7.17-7.15 (m, 2H, Ar-H), 7.02-7.00 (m, 2H, Ar-H), 2.24 (s, 6H, 2 x C*H*$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) : δ 159.9 (C), 156.5 (C), 137.8 (2 x C), 132.3 (C), 130.9 (CH), 129.2 (CH), 128.4 (CH), 127.6 (CH), 125.5 (CH), 122.6 (C), 19.6 (2 x CH_3) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3315, 1682, 1497; HRMS (ESI^+) calculated for $C_{16}H_{16}N_3O$ $[M+H]^+$ 266.1288, found: 266.1283.

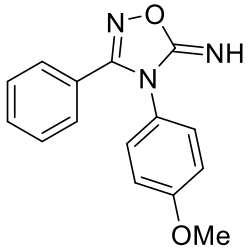
4-Phenyl-3-(thiophen-3-yl)-1,2,4-oxadiazol-5(4*H*)-imine (225)



Following general procedure 4.4: *N*-Hydroxythiophene-3-carbimidoyl chloride **6h** (100 mg, 0.62 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (210 mg, 0.77 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar under argon. The substrates were dissolved in anhydrous THF (0.5 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 °C (icebath) and TBAF (1M in THF, 1.9 mL, 1.9 mmol) was added through a syringe pump at the rate of 1.9 mL/hour. After the addition, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 10 mL ethyl acetate, and washed with water (2 x 5 mL) and brine (1 x 5 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure and purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1 to 4:6) to afford the product **1h** (80 mg, 54% yield) yield as a yellow solid, 54% yield; M. p. 131-132 °C; R_f 0.30 (1:1 Pet Ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.49 (m, 3H, Ar-H), 7.36- 7.34 (m, 2H, Ar-H), 7.31-7.29 (m, 1H, HetAr-H), 7.14-7.13 (m, 2H, HetAr-H), 5.27 (brs, 1H, N*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) : δ 160.8 (C), 153.2 (C), 133.0 (C), 130.1 (CH), 129.9 (CH), 128.1 (CH), 128.0 (CH),

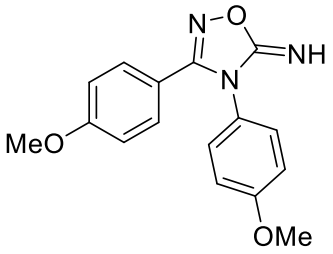
126.7 (CH), 126.1 (CH), 123.3 (C) ppm; IR: ῡ (cm^{-1}) 3303, 3102, 2923, 1679, 1538, 1438; HRMS (ESI) calculated for $C_{12}H_{10}N_3OS$ $[M+H]^+$ 244.0539, found: 244.0546.

4-(4-Methoxyphenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-imine (226)



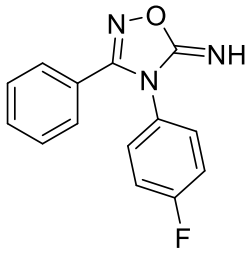
Following general procedure 4.4: *N*-Hydroxybenzimidoyl chloride **6a** (20 mg, 0.13 mmol) and *N*-(4-Methoxyphenyl) *N*-toluenesulfonyl cyanamide **2b** (50 mg, 0.16 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar under argon. The substrates were dissolved in anhydrous THF (0.3 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 °C (ice-bath) and TBAF (1M in THF, 0.4 mL, 0.4 mmol) was added through a syringe pump at the rate of 0.4 mL/hour. After the addition, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 10 mL ethyl acetate, and washed with water (2 x 5 mL) and brine (1 x 5 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure and purified by column chromatography on silica gel using Pet Ether:EtOAc (8:2 to 4:6) to afford the product **1i** (23 mg, 68% yield) as a yellow solid, 68% yield; M. p. 126-128 °C; R_f 0.31 (1:1 Pet Ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.43 (m, 1H, Ar-H), 7.38-7.32 (m, 4H, Ar-H), 7.20-7.16 (m, 2H, Ar-H), 6.96-6.92 (m, 2H, Ar-H), 3.82 (s, 1H, OC$\underline{H}_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) : δ 161.3 (C), 159.9 (C), 157.1 (C), 131.5 (CH), 128.9 (CH), 128.8 (CH), 128.2 (CH), 125.6 (C), 123.2 (C), 115.2 (CH), 55.5 (O$\underline{C}H_3$) ppm; IR: ῡ (cm^{-1}) 3301, 2923, 2852, 1679, 1512; HRMS (ESI^+) calculated for $C_{15}H_{14}N_3O_2$ $[M+H]^+$ 268.1081, found: 268.1090.

3,4-bis (4-Methoxyphenyl)-1,2,4-oxadiazol-5(4*H*)-imine (227)



Following general procedure 4.4: *N*-Hydroxy-4-methoxybenzimidoyl chloride **6c** (25 mg, 0.13 mmol) and *N*-(4-Methoxyphenyl) *N*-toluenesulfonyl cyanamide **2b** (50 mg, 0.16 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar under argon. The substrates were dissolved in anhydrous THF (0.3 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 °C (ice-bath) and TBAF (1M in THF, 0.4 mL, 0.4 mmol) was added through a syringe pump at the rate of 0.4 mL/hour. After the addition, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 10 mL ethyl acetate, and washed with water (2 x 5 mL) and brine (1 x 5 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure and purified by column chromatography on silica gel using Pet Ether:EtOAc (8:2 to 2:8) to afford the product 1j (25 mg, 62% yield) as a yellow solid, 62% yield; M. p. 125-127 °C; R_f 0.20 (1:1 Pet Ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.28 (m, 2H, Ar-H), 7.20-7.16 (m, 2H, Ar-H), 6.97-6.93 (m, 2H, Ar-H), 6.85-6.81 (m, 2H, Ar-H), 3.83 (s, 3H, OC$\underline{H}_3$), 3.80 (s, 3H, OC$\underline{H}_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9 (2 x C), 159.9 (C), 156.9 (C), 129.8 (CH), 128.9 (CH), 125.9 (C), 115.2 (C), 115.1 (CH), 114.2 (CH), 55.5 (OCH_3), 55.3 (OCH_3); IR: $\tilde{\upsilon}$ (cm^{-1}) 3331, 3245, 2926, 1676, 1606, 1511; HRMS (ESI^+) calculated for $C_{16}H_{16}N_3O_3$ $[M+H]^+$ 298.1186, found: 298.1178.

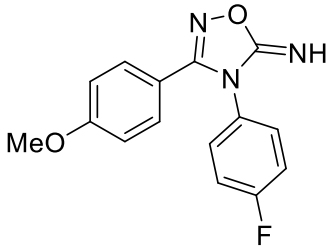
4-(4-Fluorophenyl)-3-phenyl-1,2,4-oxadiazol-5(4*H*)-imine (228)



Following general procedure 4.4: *N*-Hydroxybenzimidoyl chloride **6a** (25 mg, 0.13 mmol) and *N*-(4-Fluorophenyl) *N*-toluenesulfonyl cyanamide **2c** (50 mg, 0.17 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar under argon. The substrates were dissolved in anhydrous THF (0.3 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 °C (ice-bath) and TBAF (1M in THF, 0.41 mL, 0.41 mmol) was added through a syringe pump at the rate of 0.41 mL/hour. After the addition, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 10 mL ethyl acetate, and washed with water (2 x 5 mL) and brine (1 x 5 mL). The organic fraction was dried over anhydrous

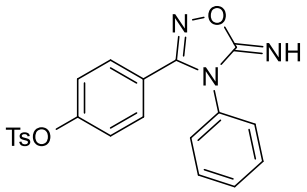
Na_2SO_4 and solvents removed under reduced pressure and purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1 to 1:1) to afford the product **1k** (30 mg, 89% yield) as a white solid, 89% yield; M. p. 101-103 °C; R_f 0.50 (1:1 Pet Ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.46 (m, 1H, Ar-H), 7.37-7.32 (m, 4H, Ar-H), 7.26-7.24 (m, 2H, Ar-H), 7.14-7.11 (m, 2H, Ar-H), 5.70 (brs, 1H, N*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.4 (C, d, J = 250 Hz), 160.1 (C), 157.0 (C), 131.7 (CH), 129.4 (CH, d, J = 9.1 Hz), 129.2 (C, d, J = 2.7 Hz), 128.9 (CH), 128.3 (CH), 122.9 (C), 117.0 (CH, d, J = 22.7 Hz) ppm; IR: ῡ (cm^{-1}) 3343, 2923, 1686, 1509; HRMS (ESI) calculated for $C_{14}H_{11}FN_3O$ $[M+H]^+$ 256.0881, found: 256.0885.

4-(4-fluorophenyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazol-5(4*H*)-imine (229)



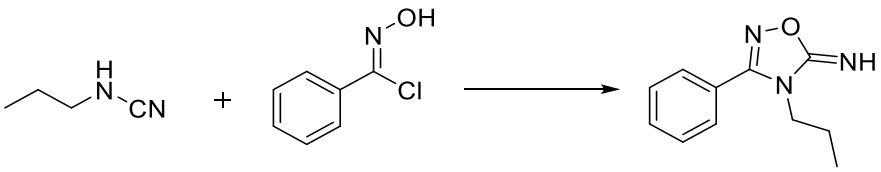
Following general procedure 4.4: *N*-Hydroxy-4-methoxybenzimidoyl chloride **6c** (21 mg, 0.13 mmol) and *N*-(4-Fluorophenyl) *N*-toluenesulfonyl cyanamide **2b** (50 mg, 0.17 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar under argon. The substrates were dissolved in anhydrous THF (0.3 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 °C (ice-bath) and TBAF (1M in THF, 0.4 mL, 0.4 mmol) was added through a syringe pump at the rate of 0.4 mL/hour. After the addition, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 10 mL ethyl acetate, and washed with water (2 x 5 mL) and brine (1 x 5 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure and purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1 to 6:4) to afford the product **1l** (36 mg, 96 % yield) as a yellow solid, 96 % yield; M. p. 117-120 °C; R_f 0.51 (1:1 Pet Ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.26 (m, 4H, Ar-H), 7.17-7.13 (m, 2H, Ar-H), 6.89-6.84 (m, 2H, Ar-H), 3.82 (s, 3H, OC*H*$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4 (C, d, J = 250 Hz), 162.1 (C), 160.7 (C),156.8 (C), 129.8 (CH), 129.56 (CH, d, J = 8.7 Hz), 129.4 (C, d, J =2.9 Hz), 116.9 (CH, d, J = 23.4 Hz), 114.8 (C), 114.3 (CH), 55.3 (OCH_3) ppm; IR: ῡ (cm^{-1}) 3313, 2921, 2850, 1684, 1603, 1513; HRMS (ESI^+) calculated for $C_{15}H_{13}FN_3O_2$ $[M+H]^+$ 286.0986, found: 286.0984.

3-(4-toluenesulfonyl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-imine (230)



Following general procedure 4.4: *N*-Hydroxy-4-hydroxybenzimidoyl chloride **6c** (21 mg, 0.13 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2b** (50 mg, 0.17 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar under argon. The substrates were dissolved in anhydrous THF (0.3 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 °C (ice-bath) and TBAF (1M in THF, 0.4 mL, 0.4 mmol) was added through a syringe pump at the rate of 0.4 mL/hour. After the addition, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 10 mL ethyl acetate, and washed with water (2 x 5 mL) and brine (1 x 5 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure and purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1 to 6:4) to afford the product **1l** (36 mg, 43 % yield) as a pale yellow solid, 43% yield; M. p. 138-139 °C; R_f 0.21 (1:1 Pet Ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, J = 7.9 Hz, 2H, Ar-H), 7.44 (brs, 3H, Ar-H), 7.30-7.27 (m, 4H, Ar-H), 7.23-7.19 (m, 2h, Ar-H), 6.97 (d, J = 8.4 Hz, 2H, Ar-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) : δ 160.2 (C), 156.1 (C), 151.7 (C), 145.8 (C), 132.9 (C), 131.9 (C), 129.9 (CH), 129.7 (CH), 128.4 (CH), 127.4 (CH), 122.9 (CH), 121.9 (C), 21.7 (CH_3) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3315, 1681, 1537, 1433, 1371, 1156; HRMS (ESI) calculated for $C_{21}H_{18}N_3O_4S$ $[M+H]^+$ 408.1013, found: 408.1034.

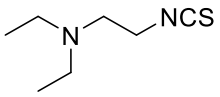
3-Phenyl-4-propyl-1,2,4-oxadiazol-5(4*H*)-imine (253)



Following general procedure 4.4: *N*-Hydroxybenzimidoyl chloride **6a** (100 mg, 0.64 mmol) and *N*-propyl cyanamide **2d** (67 mg, 0.80 mmol) were taken in an oven dried 10 mL round bottom flask equipped with a magnetic stirrer bar under argon. The substrates were dissolved in anhydrous THF (0.5 mL) and allowed to stir for 5 minutes. The reaction mixture was cooled to 0 °C (ice-bath) and TBAF (1M in THF, 1.92 mL, 1.92 mmol) was added through a syringe

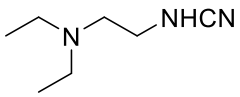
pump at the rate of 1.92 mL/hour. After the addition, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was purified by column chromatography on neutralized silica gel using Pet Ether:EtOAc (8:2) to afford the product **1m** (45 mg, 35% yield) as a yellow oil, 35 % yield; R_f 0.45 (2:3 Pet ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60-7.56 (m, 5H, Ar-H), 3.60 (brt, J = 6.7 Hz, 2H, C$\underline{H}_2$), 1.71-1.67 (m, 2H, C$\underline{H}_2$), 0.84 (brt, J = 7.0 Hz, 3H, C$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8 (C), 131.7 (CH), 129.3 (CH), 128.4 (CH), 123.6 (C), 44.9 (CH_2), 21.1 (CH_2), 10.8 (CH_3) ; IR ῡ (cm $^{-1}$): 2951, 2832, 1689, 1493, 1452; HRMS (ESI) calculated for $C_{11}H_{14}N_3O$ $[M+H]^+$ 204.1151, found: 204.1131.

2-(*N*,*N*-Diethylamino)ethyl isothiocyanate (266)[9]



Diethylethylenediamine (**265**, 4.3 mmol) in acetone (4 mL) was cooled to -10 °C in a dry ice/acetone bath. Carbon disulfide (1.1 equiv., 4.73 mmol) in acetone (4 mL) was added dropwise via an addition funnel over 15 min. Then, over 45 min, the temperature was allowed to slowly rise to 10 °C. The reaction mixture was then cooled to -15 °C. Over 45 min, a solution of $HgCl_2$ (1.0 equiv, 4.3 mmol) in acetone (12 mL) was added, keeping the temperature below -10 °C. After warming to 0 °C over 15 min, Et_3N (2.2 equiv, 9.46 mmol) was added slowly by syringe. Finally, the reaction mixture was refluxed for 1 h, becoming black. Upon cooling, the salts were filtered through Celite, and washed subsequently with acetone (1 × 50 mL) and ether (2 × 50 mL). The filtrate was treated with Na_2SO_4. Solvent was removed by rotary evaporation. To the residue was added ether (75 mL), and this was filtered. The filtrate was concentrated to yield **266** as a colourless oil in 61 % yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.52 (t, J = 6.6 Hz, 2H, CH_2), 2.75 (t, J = 6.6 Hz, 2H, CH_2), 2.58 (q, J = 7.2 Hz, 4H, 2 x CH_2), 1.04 (t, J = 7.2 Hz, 6H, 2 x CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 131.4 (C), 52.5 (CH_2), 47.4 (CH_2), 44.0 (CH_2), 12.1 (CH_3) ppm; IR: ῡ (cm^{-1}) 2968, 2809, 2082, 1445.

2-(*N*,*N*-Diethylamino)ethyl cyanamide (241)

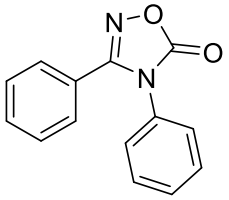


25% aqueous NH_3 (0.8 mL) was added drop wise to 2-(*N*,*N*-Diethylamino)ethyl isothiocyanate (**266**, 0.63 mmol) in ethyl acetate (1 mL) to give a thiourea product. After stirring for 10 minutes at room temperature the excess of NH_3 was removed in a rotary evaporator whereby the solvent ethylacetate was also simultaneously removed leaving behind the aqueous layer. To the crude reaction mixture was then further added ethyl acetate (1 mL) and triethylamine (0.11 ml, 1.14 mmol). To the resultant solution, iodine (144 mg, 0.57 mmol) was added in small pinches, during which precipitation of elemental sulfur was observed. Completion of the reaction was confirmed by TLC. The precipitated sulfur was filtered, washed with ethyl acetate (2 x 5 mL). The organic layer was washed with water (2 x 5 mL) and dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified over a short column of silica gel eluting it with hexane: ethyl acetate (97:3) to give the pure product in 15 % yield; colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.15 (t, J = 5.7 Hz, 2H, CH_2), 2.68 (br s, 1H, N*H*), 2.59 (t, J = 5.7 Hz, 2H, CH_2), 2.52 (q, J = 7.2 Hz, 4H, 2 x CH_2), 1.01 (t, J = 7.2 Hz, 6H, 2 x CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 116.7 (CN), 51.2 (CH_2), 46.5 (CH_2), 43.6 (CH_2), 11.8 (CH_3) ppm; IR: ῡ (cm^{-1}) 2964, 2216

4.5 Synthesis of 1,2,4-oxadiazol-5-ones from 1,2,4-oxadiazol-5(4*H*)-imines

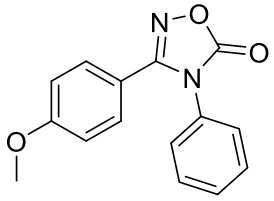
1,2,4-oxadiazol-5(4*H*)-imine (1 equiv., 0.42 mmol) was taken in an oven-dried round bottom flask, and dissolved in 1 mL methanol. 0.6 mL of conc. HCl was added to the reaction mixture and refluxed for 3-5 hours. After the complete conversion of the starting material (TLC), methanol was removed under vacuum and the residue was dissolved in ethyl acetate (20 mL), and neutralised with sat. (aq) $NaHCO_3$. The ethyl acetate fraction was further washed with water (2 x 10 mL) and brine (1 x 10 mL), dried over anhydrous Na_2SO_4. The organic fraction was removed under vacuum and the residue purified by column chromatography.

3,4-Diphenyl-1,2,4-oxadiazol-5(4*H*)-one (216)



Following general procedure 4.5: 3,4-Diphenyl-1,2,4-oxadiazol-5(4*H*)-imine **1a** (230 mg, 0.97 mmol) was taken in an oven-dried round bottom flask, and dissolved in 1.5 mL methanol. 1.4 mL of concd. HCl was added to the reaction mixture and refluxed for 5 hours. The reaction mixture was cooled to room temperature, methanol was removed under vacuum and the residue was dissolved in ethyl acetate (30 mL), and neutralized with sat. (aq) $NaHCO_3$ solution. The ethyl acetate fraction was separated and further washed with water (2 x 10 mL), brine (1 x 10 mL) and dried over anhydrous Na_2SO_4. The volatile solvent was removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1) to afford the product **4a** (220 mg, 95% yield) as a white solid, 95% yield; M. p. 168-169 °C (Lit-166-167 °C)[4]; R_f 0.33 (9:1 Pet ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.48 (m, 1H, Ar-H), 7.47-7.44 (m, 3H, Ar-H), 7.38-7.35 (m, 4H, Ar-H), 7.25-7.23 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3 (C), 157.5 (C), 132.0 (C), 131.9 (CH), 129.8 (CH), 129.5 (CH), 128.9 (CH), 128.2 (CH), 126.8 (CH), 123.0 (C); IR: $\tilde{\upsilon}$ (cm^{-1}) 3065, 2922, 2852, 1770, 1553; HRMS (ESI^+) calculated for $C_{14}H_{11}N_2O_2$ $[M+H]^+$ 239.0815, found: 239.0820.

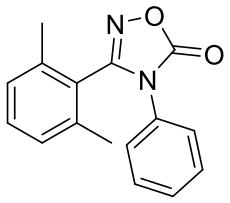
3-(4-Methoxyphenyl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-one (231)



Following general procedure 4.5: 3-(4-Methoxyphenyl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-imine **1c** (45 mg, 0.17 mmol) was taken in an oven-dried round bottom flask, and dissolved in 0.5 mL methanol. 0.3 mL of concd. HCl was added to the reaction mixture and refluxed for 4 hours. The reaction mixture was cooled to room temperature, methanol was removed under vacuum and the residue was dissolved in ethyl acetate (20 mL), and neutralized with sat. (aq) $NaHCO_3$ solution. The ethyl acetate fraction was separated and further washed with water (2 x 10 mL), brine (1 x 10 mL) and dried over anhydrous Na_2SO_4. The volatile solvent was removed under vacuum and the residue purified by column chromatography on silica gel using Pet

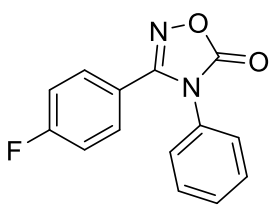
Ether:EtOAc (9:1) to afford the product **4c** (37 mg, 86% yield) as a white solid, 86 % yield; M. p. 160-162 °C; R_f 0.15 (9:1 Pet ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.47 (m, 3H, Ar-H), 7.33-7.29 (m, 2H, Ar-H), 7.28-7.25 (m, 2H, Ar-H), 6.90-6.86 (m, 2H, Ar-H), 3.84 (s, 3H, OC*H*$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4 (C), 158.4 (C), 157.2 (C), 132.1 (C),129.7 (2 x CH), 129.5 (CH), 126.9 (CH), 114.9 (C), 114.4 (CH), 55.4 (OCH_3) ppm; IR: ῡ (cm^{-1}) 3002, 2934, 2836, 1770, 1585,; HRMS (ESI) calculated for $C_{15}H_{13}N_2O_3$ $[M+H]^+$ 269.0921, found: 269.0911.

3-(2,6-Dimethylphenyl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-one (232)



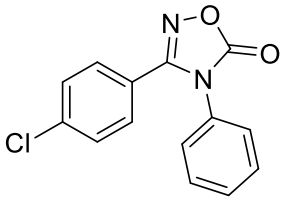
Following general procedure 4.5: 3-(2,6-Dimethylphenyl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-imine **1g** (80 mg, 0.30 mmol) was taken in an oven-dried round bottom flask, and dissolved in 1.0 mL methanol. 0.6 mL of conc. HCl was added to the reaction mixture and refluxed for 6 hours. The reaction mixture was cooled to room temperature, methanol was removed under vacuum and the residue was dissolved in ethyl acetate (20 mL), and neutralized with sat. (aq) $NaHCO_3$solution. The ethyl acetate fraction was further washed with water (2 x 10 mL), brine (1 x 10 mL) and dried over anhydrous Na_2SO_4. The volatile solvent was removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1) to afford the product **4g** (72 mg, 91% yield) as awhite solid, 91 % yield; M. p. 137-138 °C; R_f 0.38 (9:1 Pet ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.33(m, 3H, Ar-H), 7.31-7.29 (m, 1H, Ar-H), 7.15-7.13 (m, 2H, Ar-H), 7.10, (brs, 1H, Ar-H), 7.08 (brs, 1H, Ar-H), 2.26 (s, 6H, 2 x C*H*$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9 (C), 157.3 (C), 138.1 (2 x C), 131.4 (CH),129.4 (CH), 128.9 (CH), 127.9 (CH), 124.8 (CH), 122.7 (C), 19.8 (2 x CH_3) ppm; IR: ῡ (cm^{-1}) 2922, 2853, 1769, 1571; HRMS (ESI) calculated for $C_{16}H_{15}N_2O_2$ $[M+H]^+$ 267.1128, found: 267.1125.

3-(4-Fluorophenyl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-one (233)



Following general procedure 4.5: 3-(4-Fluorophenyl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-imine **1e** (73 mg, 0.28 mmol) was taken in an oven-dried round bottom flask, and dissolved in 1.0 mL methanol. 0.6 mL of conc. HCl was added to the reaction mixture and refluxed for 6 hours. The reaction mixture was cooled to room temperature, methanol was removed under vacuum and the residue was dissolved in ethyl acetate (20 mL), and neutralized with sat. (aq) $NaHCO_3$ solution. The ethyl acetate fraction was separated and further washed with water (2 x 10 mL) and brine (1 x 10 mL), dried over anhydrous Na_2SO_4. The volatile solvent was removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1) to afford the product **4e** (66 mg, 90% yield) as a white solid, 90 % yield; M. p. 166-167 °C; R_f 0.28 (9:1 Pet ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.46 (m, 3H, Ar-H), 7.40-7.35 (m, 2H, Ar-H), 7.25-7.21 (m, 2H, Ar-H), 7.10-7.04 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6 (C, d, *J* = 254.5 Hz), 158.2 (C), 156.6 (C), 131.8 (C), 130.45 (CH, d, *J = 8.43 Hz*), 129.9 (2 x CH), 129.7 (CH), 126.9 (CH), 119.16 (C, d, *J* = 3.8 Hz), 116.4 (CH, d, *J* = 23 Hz) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 2924, 1769, 1605, 1513; HRMS (ESI) calculated for $C_{14}H_{10}FN_2O_2$ $[M+H]^+$ 257.0721, found: 257.0722.

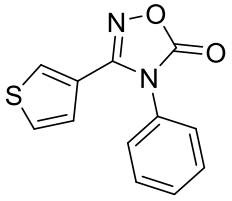
3-(4-Chlorophenyl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-one (234)



Following general procedure 4.5: 3-(4-Chlorophenyl)-4-phenyl-1,2,4-oxadiazol-5(4*H*)-imine **1d** (73 mg, 0.27 mmol) was taken in an oven-dried round bottom flask, and dissolved in 1 mL methanol. 0.6 mL of conc. HCl was added to the reaction mixture and refluxed for 3 hours. The reaction mixture was cooled to room temperature, methanol was removed under vacuum and the residue was dissolved in ethyl acetate (20 mL), and neutralized with sat. (aq) $NaHCO_3$ solution. The ethyl acetate fraction was separated and further washed with water (2 x 10 mL), brine (1 x 10 mL) and dried over anhydrous Na_2SO_4. The volatile solvent was removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether:EtOAc (9.5:0.5) to afford the product **4d** (69 mg, 95% yield) as a white solid, 95 % yield; M. p. 182-183 °C; R_f 0.33 (9:1 Pet ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.46 (m, 3H, Ar-H), 7.37-7.34 (m, 2H, Ar-H), 7.32-7.28 (m, 2H, Ar-H), 7.21-7.24 (m, 2H, Ar-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0 (C), 156.6 (C), 138.4 (C), 131.7 (C),129.9 (CH),

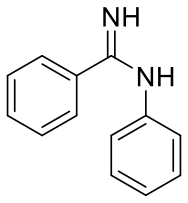
129.7 (CH), 129.4 (CH), 129.3 (CH), 126.8 (CH), 121.4 (C); IR: ῡ (cm^{-1}) 2922, 2853, 1770, 1583; HRMS (ESI) calculated for $C_{14}H_{10}ClN_2O_2$ $[M+H]^+$ 273.0425, found: 273.0427.

4-Phenyl-3-(thiophen-3-yl)-1,2,4-oxadiazol-5(4*H*)-one (235)



Following general procedure 4.5: 4-Phenyl-3-(thiophen-3-yl)-1,2,4-oxadiazol-5(4*H*)-imine 1h (45 mg, 0.18 mmol) was taken in an oven-dried round bottom flask, and dissolved in 0.5 mL methanol. 0.3 mL of conc. HCl was added to the reaction mixture and refluxed for 5 hours. The reaction mixture was cooled to room temperature, methanol was removed under vacuum and the residue was dissolved in ethyl acetate (20 mL), and neutralized with sat. (aq) $NaHCO_3$ solution. The ethyl acetate fraction was separated and further washed with water (2 x 10 mL) and brine (1 x 10 mL), dried over anhydrous Na_2SO_4. The volatile solvent was removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether:EtOAc (9.5:0.5) to afford the product **4h** (40 mg, 89% yield) as a white solid, 89 % yield; M. p. 170-171 °C; R_f 0.23 (9:1 Pet ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.52 (m, 3H, Ar-H), 7.36-7.33 (m, 3H, Ar-H), 7.22 (dd, J = 2.9, 1.3 Hz, 1H, HetAr-H), 7.17 (dd, J = 5.2, 1.3 Hz, 1H, HetAr-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2 (C), 153.7 (C), 131.8 (C), 130.2 (CH),130.1 (CH), 128.5 (CH), 127.5 (CH), 127.1 (CH), 125.9 (CH), 123.3 (C) ppm; IR: ῡ (cm^{-1}) 3119, 2922, 1764, 1581, 1453; HRMS (ESI) calculated for $C_{12}H_9N_2O_2S$ $[M+H]^+$ 245.0379, found: 245.0377.

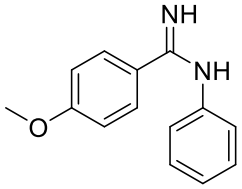
4.6 Synthesis of *N*-Phenylbenzimidamide (236)[9]



1,2,4-Oxadiazol-5-one was taken in a 10 mL oven dried round bottom flask (1 equiv, 0.25 mmol) and dissolved in 0.8 mL ethyl acetate followed by addition of glacial acetic acid (1 equiv, 0.25 mmol). Pd/C catalyst was added and mixture stirred under a hydrogen atmosphere (1.1 atm) at room temperature for 20 hours. The reaction mixture was diluted with ethyl acetate

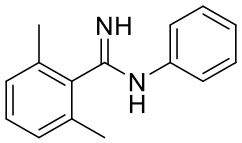
(10 mL), and filtered through celite. The filtrate was neutralised with aq. $NaHCO_3$, and washed with water (2x 5 mL) and brine (1 x 5 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvent removed under vacuum. The residue was purified by silica gel column chromatography (DCM-methanol) to give *N*-Phenylbenzimidamide[10] in 94% yield; yellow solid; M. p. 110-111 °C (lit- 110 – 111.2 °C)[7]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (brs, 2H, Ar-H), 7.50-7.43 (m, 3H, Ar-H), 7.38-7.35 (m, 2H, Ar-H), 7.09-7.06 (m, 1H. Ar-H), 7.0 (brd, J = 7.93 Hz, 2H, Ar-H), 4.86 (brs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.2 (C), 130.8 (CH), 129.5 (CH), 128.6 (CH), 126.9 (CH), 127.3 (C), 123.3 (CH), 121.8 (CH) ppm; IR: ῡ (cm^{-1}) 3318, 3058, 1619, 1571, 1475, 1433; HRMS (ESI) calculated for $C_{13}H_{12}N_2Na$ $[M+Na]^+$ 219.0893, found: 219.0882.

4-methoxy-*N*-phenylbenzimidamide (237)



Following procedure 4.6: white solid, 91% yield; M. p. 144-146 °C (lit- 144-147 °C)[7]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (brs, 2H, Ar-H), 7.37-7.29 (m, 2H, Ar-H), 7.14 (t, d = 7.2 Hz, 1H, Ar-H), 7.01 (d, d = 6.4 Hz, 2H, Ar-H), 6.93 (d, J = 7.9 Hz, 2H, Ar-H), 3.85 (s, 3H, OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 129.6 (CH), 114.2 (CH), 55.5 (OCH_3) ppm; IR: ῡ (cm^{-1}) 3318, 3058, 1619, 1571, 1475, 1433; HRMS (ESI) calculated for $C_{14}H_{15}N_2O$ $[M+H]^+$ 227.1179, found: 227.1190.

2,4-dimethyl-*N*-phenylbenzimidamide (238)

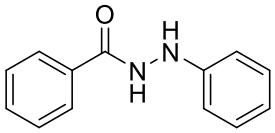


Following procedure 4.6: brown solid, 89% yield; M. p. 125-127 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.27 (m, 3H, Ar-H), 7.20-6.99 (m, 5H, Ar-H), 6.85-6.78 (br m, 1H, Ar-H), 2.45-2.22 (m, 6H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.3 (CH), 131.2 (CH), 129.1 (CH), 128.3 (CH), 127.6 (CH), 122.0 (CH), 19.4 (CH_3) ppm; IR: ῡ (cm^{-1}) 3318, 3058, 1619, 1571, 1475, 1433; HRMS (ESI) calculated for $C_{15}H_{17}N_2$ $[M+H]^+$ 225.1386, found: 225.1391.

4.7 Experimental for Ch-3 - Synthesis of acyl hydrazides:

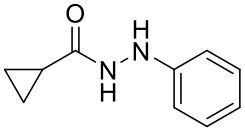
4.7.1 Method A: Synthesis of acyl hydrazides starting from acyl chlorides[12]

***N'*-Phenylbenzohydrazide[12] (300)**



To a stirred solution of 2.16 g (20 mmol) phenylhydrazine in 20 mL dichloromethane was slowly added pyridine (1.58 g, 20 mmol) under the ice bath. Then, to this, well-stirred reaction mixture was added dropwise a solution of benzoyl chloride (2.8 g, 20 mmol) in dichloromethane (5 mL) over a period of 2 h. Upon completion of addition, ice bath was taken away, and the stirring was continued for another 3 h at the room temperature. A solid was collected by filtration, washed with water, dried, and recrystallised with ethanol to give 3.6 g of compound **300** (yield 85%) ; δ_H (500 MHz, MeOD) 7.95-7.91 (m, 2 H, Ar-H), 7.61-7.55 (m, 1 H, Ar-H), 7.53-7.47 (m, 2 H, Ar-H), 7.20-7.10 (m, 2 H, Ar-H), 6.80 (d, *J* = 7.8 Hz, 2 H, Ar-H), 6.72 (t, *J* = 7.3 Hz, 1 H, Ar-H); δ_C (100 MHz, MeOD) 166.3 (C), 149.5 (C), 133.0 (C), 131.5 (CH), 128.7 (CH), 128.4 (CH), 127.2 (CH), 118.6 (CH), 112.3 (CH); IR: $\tilde{\upsilon}$ (cm^{-1}) (neat) 3298, 3090, 1629, 1594, 1554, 1488.

***N'*-phenylcyclopropanehydrazide (309)[13]**



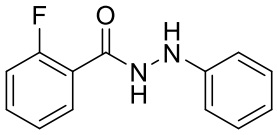
Following method A: Cyclopropylcarbonyl chloride (2.5 g, 23.9 mmol) and phenyl hydrazine (2.58 g, 23.9 mmol) were reacted to afford the product **309** (2.19 g, 52 % yield) as a pale-yellow solid; δ_H (500 MHz, $CDCl_3$) 7.39 (s, 1 H, N*H*), 7.30-7.21 (m, 2 H, Ar-H), 6.96-6.83 (m, 3 H, Ar-H), 6.11 (s, 1 H, N*H*), 1.49-1.44 (m, 1 H, CH), 1.07-1.03 (m, 2 H, CH_2), 0.86-0.78 (m, 2 H, CH_2); δ_C (125 MHz, $CDCl_3$) 173.9 (C=O), 148.1 (C), 129.2 (CH), 121.2 (CH), 113.6 (CH), 112.6 (CH), 12.8 (CH), 7.5 (CH_2); IR: $\tilde{\upsilon}$ (cm^{-1}) (neat) 3298, 3090, 1629, 1594, 1554, 1488

4.7.2 Method B: Synthesis of acyl hydrazides from carboxylic acids[14]

In a 50 ml round bottom flask, phenylhydrazine (1.0 equiv), 2-flourobenzoic acid (1.42 g, 10.1 mmol, 1.0 equiv) and EDC.HCl (1.3 equiv) were dissolved in MeCN (10 mL) and stirred vigorously at ambient temperature. Immediately afterwards, DIPEA (2.0 equiv) was added in

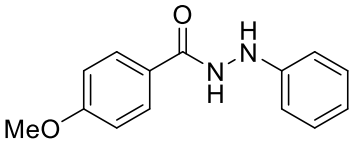
a single portion and the reaction mixture was monitored by HPLC and LCMS until completion. Once finished, 100 mL of 1 M HCl (ice-cold) were added slowly at 0 °C. Afterwards, the organic components were extracted by ethyl acetate (3x 100 mL). The organic layer was washed with 1 M HCl (100 mL), 100 ml $NaHCO_3$ (sat.) (3x 100 mL), brine (3x 100 mL) and water (60 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on a rotator evaporated at 40 °C (100 mBar). The white solid was further purified by gradient elution flash column chromatography on silica gel using ethyl acetate/cyclohexane as solvent system (0-50 %, over 60 min), giving ***N*-phenyl-4- fluorobenzohydrazide (302)** as a white solid (1.82 g, 7.90 mmol, 79 % yield).

***N'*-Phenyl-2-fluorobenzohydrazide (302)**



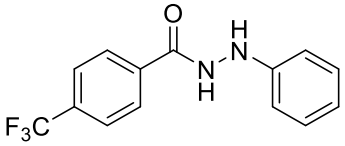
Yellow solid, 79% yield; ^{1}H NMR (500 MHz, MeOD): δ 7.75 (td, J = 7.5, 1.6 Hz, 1H, Ar-H), 7.60-7.55 (m, 1H, Ar-H), 7.33-7.19 (m, 4H, Ar-H), 6.91 (d, J = 7.6 Hz, 2H, Ar-H), 6.83 (t, J = 7.4 Hz, 1H, Ar-H) ppm; ^{13}C NMR (120 MHz, MeOD) : δ 167.2 (C=O), 145.5 (C, d, J = 250.7 Hz), 149.9 (C), 134.4 (CH, d, J = 8.2 Hz), 131.5 (CH), 130.0 (CH), 125.8 (d, J = 4 Hz, CH), 123.1 (d, J = 14.5 Hz, C), 121.2 (CH), 117.3 (d, J = 22.7 Hz, CH), 114.2 (CH) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3265, 1637, 1613.

***N'*-Phenyl-4-methoxybenzohydrazide (301)[14]**



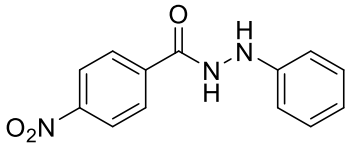
Following Method B: 4-methoxybenzoic acid (2.5 g, 16.4 mmol) and phenyl hydrazine (1.77 g, 16.4 mmol) were reacted to afford the product **301** (3.42 g, 86 % yield) as a light yellow solid; δ_H (500 MHz, MeOD) 7.89-7.86 (m, 2 H, Ar-H), 7.20-7.17 (m, 2H, Ar-H), 7.04-7.01 (m, 2H, Ar-H)), 6.88-6.86 (m, 2H, Ar-H), 6.81 (t, J = 7.3 Hz, 1H, Ar-H), 3.86 (3 H, s, CH_3); δ_C (125 MHz, MeOD) 169.9 (C=O), 164.3 (C), 150.3 (C), 130.3 (CH), 130.0 (CH), 126.1 (C), 121.1 (CH), 114.9 (CH), 114.2 (CH), 55.6 (CH_3); IR: $\tilde{\upsilon}$ (cm^{-1}): 3291, 1634, 1600.

***N'*-Phenyl-4-trifluoromethylbenzohydrazide (303)**



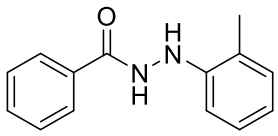
Following method B: 4-trifluoromethoxybenzoic acid (1.0 g, 5.26 mmol) and phenyl hydrazine (0.57 g, 5.26 mmol) were reacted to afford the product **301** (1.25 g, 85 % yield) as a orange solid; δ_H (500 MHz, MeOD) 8.07 (d, *J* = 8.1 Hz, 2 H, Ar-H), 7.83 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.21 (t, *J* = 7.9 Hz, 2H, Ar-H), 6.89 (d, *J* = 8.2 Hz, 2H, Ar-H), 6.84 (t, *J* = 7.3 Hz, 1H, Ar-H); δ_C (125 MHz, MeOD) 168.8 (C=O), 150.0 (C), 134.4 (*J* = 32.7 Hz, C), 130.0 (CH), 129.3 (CH), 126.7 (q, *J* = 3.6 Hz, CH), 125.9 (C), 121.2 (CH), 114.2 (CH); υ_{max}/cm^{-1} (neat) 3236, 1642, 1487

***N'*-Phenyl-4-nitrobenzohydrazide (304)[14]**



Following method B: 4-nitrobenzoic acid (3.0 g, 17.9 mmol) and phenyl hydrazine (1.94 g, 17.9 mmol) were reacted to afford the product **301** (3.74 g, 81 % yield) as a light yellow solid; δ_H (500 MHz, MeOD) 8.36 (d, *J* = 8.8 Hz, 2 H, Ar-H), 8.11 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.21 (t, *J* = 7.9 Hz 2H, Ar-H)), 6.89 (d, *J* = 7.9 Hz, 2H, Ar-H), 6.83 (t, *J* = 7.3 Hz, 1H, Ar-H); δ_C (125 MHz, MeOD) 168.2 (C=O), 151.3 (C), 149.9 (C), 140.0 (C), 130.0 (CH), 129.9 (CH), 124.8 (CH), 121.3 (CH), 114.2 (CH); υ_{max}/cm^{-1} (neat) 3280, 1637, 1596, 1511, 1495, 1341

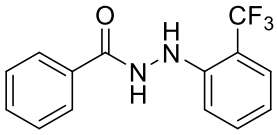
***N'*-(2-methylphenyl) benzohydrazide (305)**



Following method B: Benzoic acid (2.0 g, 16.3 mmol) and 2-methylphenyl hydrazine (2.0 g, 16.3 mmol) were reacted to afford the product **301** (1.92 g, 52 % yield) as a white solid; δ_H (500 MHz, DMSO-*d*$_6$) 10.39 (s, 1 H, N*H*), 7.94 (d, *J* = 8.5 Hz, 1 H, Ar-H), 7.51 (t, *J* = 7.4 Hz, 2 H, Ar-H), 7.25 (s, 1 H, N*H*), 7.04-7.0 (m, 2H, Ar-H), 6.73-6.67 (m, 2 H, Ar-H), 2.22 (s, 3 H, CH_3); δ_C (125 MHz, DMSO-*d*$_6$) 166.2 (C=O), 146.8 (C), 133.0 (C), 131.6 (CH), 130.0 (CH),

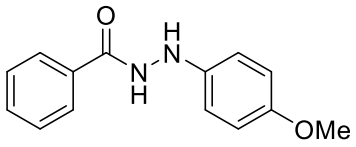
128.5 (CH), 127.2 (CH), 126.4 (CH), 122.0 (C), 118.7 (CH), 111.1 (CH), 17.2 (CH_3); υ_{max}/cm^{-1} (neat) 3277, 1643, 1604

***N'*-(2-trifluoromethylphenyl) benzohydrazide (306)**[15]



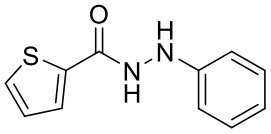
Following method B: Benzoic acid (2.0 g, 16.3 mmol) and 2-trifluoromethylphenyl hydrazine (2.9 g, 16.3 mmol) were reacted to afford the product **301** (3.76 g, 82 % yield) as a orange solid; δ_H (500 MHz, MeOD) 7.93 (d, *J* = 7.3 Hz, 2 H, Ar-H), 7.60 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.53-7.50 (m, 3H, Ar-H), 7.44 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.09 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.94 (t, *J* = 7.5 Hz, 1H, Ar-H); δ_C (125 MHz, MeOD) 170.0 (C=O), 147.6 (C), 134.3 (C), 133.8 (CH), 133.3 (CH), 129.7 (CH), 128.5 (C), 127.3 (q, *J* = 5.5 Hz, C), 125.1 (C), 120.3 (CH), 115.2 (q, *J* = 30 Hz, C), 114.4 (CH); υ_{max}/cm^{-1} (neat) 3236, 1642, 1487

***N'*-(4-methoxyphenyl) benzohydrazide (307)**[14]



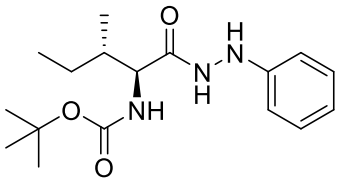
Following method B: Benzoic acid (2.0 g, 16.3 mmol) and 2-methoxyphenyl hydrazine (2.26 g, 16.3 mmol) were reacted to afford the product **301** (1.86 g, 47 % yield) as a off-white solid; δ_H (500 MHz, MeOD) 7.89-7.87 (m, 2 H, Ar-H), 7.53-7.45 (m, 2 H, Ar-H), 6.88-6.86 (m, 3 H, Ar-H), 6.78 (d, *J* = 8.8 Hz, 1H, Ar-H), 3.67 (s, 3 H, CH_3); δ_C (125 MHz, MeOD) 167.9 (C=O), 155.0 (C), 141.4 (C), 132.2 (CH), 132.1 (CH), 128.7 (C), 127.3 (CH), 116.0 (CH), 114.6 (CH), 55.6 (OCH_3); υ_{max}/cm^{-1} (neat) 3289, 1623, 1598

***N'*-Phenylthiophene-2-carbohydrazide (308)**[16]



Following method B: 2-Thiophenecarboxylic acid (2.0 g, 15.6 mmol) and phenyl hydrazine (1.68 g, 15.6 mmol) were reacted to afford the product **301** (3.27 g, 96 % yield) as a yellow solid; δ_H (500 MHz, MeOD) 7.80 (d, *J* = 3.2 Hz, 1 H, Ar-H), 7.72 (d, *J* = 4.9 Hz, 1H, Ar-H), 7.20-7.16 (m, 3H, Ar-H), 6.86 (d, *J* = 7.8 Hz, 2H, Ar-H), 6.81 (t, *J* = 7.3 Hz, 1H, Ar-H); δ_C (125 MHz, MeOD) 161.3 (C=O), 149.3 (C), 137.8 (C), 131.3 (CH), 128.7 (CH), 128.5 (CH), 128.1 (CH), 118.7 (CH), 112.2 (CH); υ_{max}/cm^{-1} (neat) 3306, 1592, 1534

***N'*-Phenyl-3-(1-tert-butoxycarbonylamino-2-methyl-butyl) carbohydrazide (310)**



Following method B: 1-tert-butoxycarbonylamino-2-methyl-butyl carboxylic acid (0.8 g, 3.4 mmol) and phenyl hydrazine (0.37 g, 3.4 mmol) were reacted to afford the product **310** (0.75 g, 68 % yield) as a light orange solid; d.r. ratio: 4:1; $[\alpha]_D$ – 37.34°; δ_H (500 MHz, MeOD) 7.14 (t, *J* = 7.5 Hz, 2 H, Ar-H), 6.84-6.77 (m, 3H, Ar-H), 3.95 (d, *J* = 7.9 Hz 1H, CH), 1.86-1.79 (br m, 1H, CH), 1.64-1.56 (m, 1H, CH), 1.47 (s, 9H, CH_3), 1.25-1.17 (m, 1H, CH), 0.98 (d, *J* = 6.7 Hz, 3H, CH_3), 0.93 (t, *J* = 7.4 Hz, 3H, CH_3); δ_C (125 MHz, MeOD) 174.5 (C=O), 157.9 (C=O), 149.8 (C), 129.8 (CH), 121.0 (CH), 114.2 (CH), 80.6 (C), 59.4 (CH), 37.8 (CH), 28.7 (CH), 26.0 (CH_2), 16.0 (CH), 11.3 (CH) ; υ_{max}/cm^{-1} (neat) 3319, 3266, 2962, 1685, 1657, 1521,

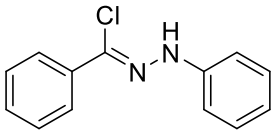
4.8 Synthesis of hydrazonyl chlorides

4.8.1 Chlorination of acyl hydrazides[17]

Carbon tetrachloride (1.46 mL, 15 mmol) was added to a stirred suspension of compound benzoyl phenylhydrazine (3.18 g, 15 mmol) and Ph_3P (4.91 g, 18.75 mmol) in acetonitrile (40 mL). Upon completion of addition, the reaction mixture was stirred at room temperature for 48 hours, and then the solution was cooled, crystallization was initiated by scratching, and the

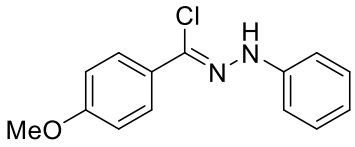
crude product was filtered off. It was further recrystallised or purified by silica-gel column chromatography.

***N*-Phenyl-benzencarbohydrazonyl chloride (70)[18]**



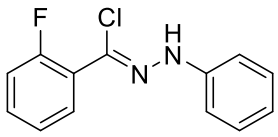
Following general procedure 4.8.1: Benzoylphenylhydrazine (3.18 g, 15 mmol) gave the product **70** (2.07 g, 60 % yield) as a buff solid; δ_H (500 MHz, $CDCl_3$) 8.06 (s, 1 H, N*H*), 7.96-7.93 (m, 2 H, Ar-H), 7.44-7.36 (m, 3 H, Ar-H), 7.33 (t, *J* = 8.5 Hz, 2 H, Ar-H), 7.21-7.18 (m, 2 H, Ar-H), 6.96 (t, *J* = 7.3 Hz, 1 H, Ar-H); δ_C (125 MHz, $CDCl_3$) 143.4 (C), 134.5 (C), 129.4 (CH), 129.2 (CH), 128.4 (CH), 126.4 (CH), 124.7 (C), 121.2 (CH), 113.5 (CH); υ_{max}/cm^{-1} (neat) 3305, 1596, 1502

***N*-Phenyl-4-methoxybenzenecarbohydrazonoyl chloride (290)[19]**



Following general procedure 4.8.1: *N'*-Phenyl-4-methoxybenzohydrazide (2 g, 8.25 mmol) gave the product **70** (1.7 g, 79 % yield) as a Buff solid; δ_H (500 MHz, $CDCl_3$) 7.95 (s, 1 H, N*H*), 7.89-7.86 (m, 2 H, Ar-H), 7.32 (app t, *J* = 7.8 Hz, 2 H, Ar-H), 7.17 (d, *J* = 7.3 Hz, 2 H, Ar-H), 6.96-6.92 (m, 3 H, Ar-H), 3.87 (s, 3 H, OCH_3); δ_C (125 MHz, $CDCl_3$) 160.5 (C), 143.6 (C), 129.3 (CH), 127.9 (CH), 127.1 (C), 124.7 (C), 120.8 (CH), 113.8 (CH), 113.3 (CH), 55.4 (OCH_3); υ_{max}/cm^{-1} (neat) 3313, 1599, 1500

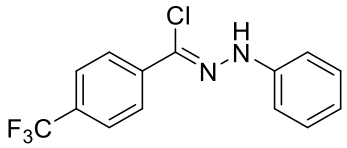
***N*-Phenyl-2-fluorobenzenecarbohydrazonoyl chloride (291)[20]**



Following general procedure 4.8.1: *N'*-Phenyl-2-fluorobenzohydrazide (1.0 g, 4.3 mmol) gave the product **70** (0.87 g, 81 % yield) as a yellow solid; δ_H (500 MHz, $CDCl_3$) 8.13 (s, 1 H, N*H*), 7.73 (td, *J* = 7.8, 1.7 Hz, 1 H, Ar-H), 7.39-7.35 (m, 1 H, Ar-H), 7.34-7.31 (m, 2 H, Ar-H), 7.23-7.14 (m, 4 H, Ar-H), 6.96 (t, *J* = 7.3 Hz, 1 H, Ar-H); δ_C (125 MHz, $CDCl_3$) 159.7 (C,

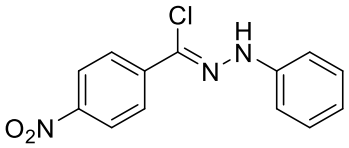
J = 257.0 Hz), 143.1 (C), 130.6 (CH, *J* = 9.1 Hz), 130.2 (CH), 129.4 (CH), 123.9 (CH, *J* = 3.6 Hz), 123.1 (C, *J* = 9.1 Hz), 121.3 (CH), 118.7 (C, *J* = 5.4 Hz), 116.5 (CH, *J* = 21.8 Hz), 113.5 (CH); υ_{max}/cm^{-1} (neat) 3302, 1579, 1499, 1239, 1132

***N*-Phenyl-4-trifluoromethylbenzenecarbohydrazonoyl chloride (292)**



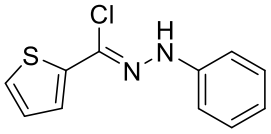
Following general procedure 4.8.1: *N'*-Phenyl-4-trifluoromethylbenzohydrazide (1.0 g, 3.5 mmol) gave the product **70** (0.53 g, 50 % yield) as a yellow solid; δ_H (500 MHz, $CDCl_3$) 8.15 (s, 1 H, N*H*), 8.04 (d, *J* = 8.2 Hz, 2 H, Ar-H), 7.67 (d, *J* = 8.2 Hz, 2 H, Ar-H), 7.35 (app t, *J* = 7.5 Hz, 2 H, Ar-H), 7.23-7.18 (m, 2 H, Ar-H), 7.0 (t, *J* = 7.3 Hz, 1 H, Ar-H); δ_C (125 MHz, $CDCl_3$) 142.8 (C), 137.7 (C), 130.7 (q, *J* = 32.7 Hz, C), 129.5 (CH), 126.4 (CH), 125.4 (CH, *J* = 3.6 Hz), 123.0 (C), 122.9 (C), 121.7 (CH); υ_{max}/cm^{-1} (neat) 3307, 1600, 1572, 1559

***N*-Phenyl-4-nitrobenzenecarbohydrazonoyl chloride (293)[21]**



Following general procedure 4.8.1: *N'*-Phenyl-4-nitrobenzohydrazide (2.0 g, 7.7 mmol) gave the product **70** (1.62 g, 76 % yield) as a orange solid; δ_H (500 MHz, $CDCl_3$) 7.95 (s, 1 H, N*H*), 7.89-7.86 (m, 2 H, Ar-H), 7.32 (app t, *J* = 7.8 Hz, 2 H, Ar-H), 7.17 (d, *J* = 7.3 Hz, 2 H, Ar-H), 6.96-6.92 (m, 3 H, Ar-H), 3.87 (s, 3 H, CH_3); δ_C (125 MHz, $CDCl_3$) 160.5 (C), 143.6 (C), 129.3 (CH), 127.9 (CH), 127.1 (C), 124.7 (C), 120.8 (CH), 113.8 (CH), 113.3 (CH), 55.4 (CH_3); υ_{max}/cm^{-1} (neat) 3315, 1603, 1547, 1503, 1334

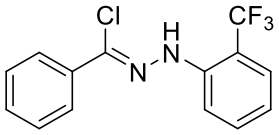
***N*-Phenyl-thiophene-2-carbohydrazonoyl chloride (297)[19]**



Following general procedure 4.8.1: *N'*-Phenylthiophene-2-carbohydrazide (2.0 g, 9.16 mmol) gave the product **70** (1.56 g, 25 % yield) as a yellow-brown solid; δ_H (500 MHz, $CDCl_3$) 7.89 (s, 1 H, N*H*), 8.04 (dd, *J* = 3.8, 1.2 Hz, 1 H, Ar-H), 7.35-7.30 (m, 3 H, Ar-H), 7.17-7.14

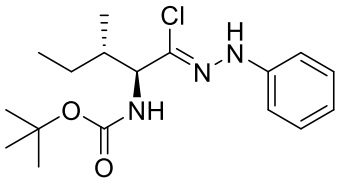
(m, 2 H, Ar-H), 7.04 (dd, *J* = 3.6, 1.4 Hz, 1 H, Ar-H), 6.96 (t, *J* = 7.3 Hz, 1 H, Ar-H); δ_C (125 MHz, $CDCl_3$) 143.0 (C), 138.7 (C), 129.3 (CH), 127.2 (CH), 127.0 (CH), 126.9 (CH), 121.2 (CH), 119.6 (C), 113.4 (CH); υ_{max}/cm^{-1} (neat) 3312, 1597, 1499

***N*-(2-Trifluoromethylphenyl)benzenecarbohydrazonoyl chloride (295)**



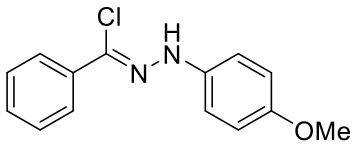
Following general procedure 4.8.1: *N'*-(2-trifluoromethylphenyl) benzohydrazide (2.0 g, 7.1 mmol) gave the product **70** (1.51 g, 71 % yield) as a orange-brown solid; δ_H (500 MHz, $CDCl_3$) 8.67 (s, 1 H, N*H*), 7.96 (dd, *J* = 8.2, 2.0 Hz, 2 H, Ar-H), 7.77 (d, *J* = 8.4 Hz, 1 H, Ar-H), 7.56-7.51 (m, 2 H, Ar-H), 7.46-7.41 (m, 3 H, Ar-H), 7.0 (t, *J* = 7.5 Hz, 1 H, Ar-H); δ_C (125 MHz, **$CDCl_3$)** 140.9 (C), 134.0 (C), 133.3 (CH), 129.8 (CH), 128.5 (CH), 127.7 (C), 126.7 (CH), 126.3 (CH, *J* = 5.5 Hz), 124.6 (C, *J* = 272.5 Hz), 120.1 (CH), 115.2 (CH), 113.3 (C, *J* = 30.9 Hz) ; υ_{max}/cm^{-1} (neat) 3375, 1610, 1584, 1518, 1313, 1095.

***N*-phenyl- (1-tertbutoxycarbonylamino-2-methylbutyl)- carbohydrazonoyl chloride (299)**



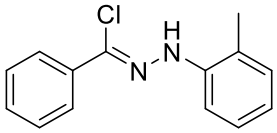
Following general procedure 4.8.1: *N'*-Phenyl-3-(1-tert-butoxycarbonylamino-2-methyl-butyl) carbohydrazide (0.5 g, 1.55 mmol) gave the product **70** (0.39 g, 74 % yield) as a light orange solid; mixture of isomers (80:20), **$[\alpha]_D$** + 19.94°; δ_H (500 MHz, $CDCl_3$) 7.69 (s, 1 H, N*H*), 7.26 (t, *J* = 7.7 Hz, 2 H, Ar-H, major), 7.19 (t, *J* = 7.8 Hz, minor), 7.05 (d, *J* = 7.8 Hz, 2H, Ar-H, major), 6.89 (d, *J* = 7.9 Hz, 1H, Ar-H, major), 6.82 (d, *J* = 7.8 Hz, minor), 4.90 (d, *J* = 8.8 Hz, 1 H, CH), 1.84 (br s, 1 H, CH), 1.63-1.54 (m, 1 H, CH_2), 1.45 (s, 9H, CH_3), 1.20-1.16 (m, 1 H, CH_2), 0.98-0.87 (m, 6 H, 2 x CH_3); δ_C (125 MHz, $CDCl_3$) 155.2 (C=O), 147.8 (C), 143.5 (C), 129.2 (CH), 120.8 (CH), 113.2 (CH), 79.8 (C), 60.8 (CH), 37.6 (CH), 28.3 (CH_3), 24.5 (CH_2), 15.7 (CH_3), 11.3 (CH_3) ; υ_{max}/cm^{-1} (neat) 3319, 3266, 2962, 1685, 1657, 1521

***N*-(4-methoxyphenyl) benzenecarbohydrazonoyl chloride (296)[21]**



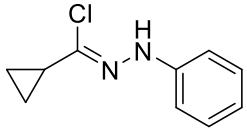
Following general procedure 4.8.1: *N'*-(4-methoxyphenyl) benzohydrazide (1.0 g, 4.1 mmol) gave the product **70** (0.78 g, 73 % yield) as a yellow-brown solid; δ_H (500 MHz, $CDCl_3$) 7.94-7.91 (m, 3 H, 2 Ar-H, 1 N*H*), 7.43-7.35 (m, 3 H, Ar-H), 7.14 (d, *J* = 8.8 Hz, 2 H, Ar-H), 6.90 (d, *J* = 9.0 Hz, 2 H, Ar-H), 3.81 (s, 3 H, OCH_3); δ_C (125 MHz, $CDCl_3$) 154.4 (C), 137.4 (C), 134.5 (C), 128.9 (CH), 128.3 (CH), 126.2 (CH), 123.8 (C), 114.7 (CH), 114.5 (CH), 55.6 (OCH_3); υ_{max}/cm^{-1} (neat) 3325, 1592, 1495

***N*-(2-methylphenyl) benzenecarbohydrazonoyl chloride[20]**



Following general procedure 4.8.1: *N'*-(2-methylphenyl) benzohydrazide (1.0 g, 4.4 mmol) gave the product **70** (0.6 g, 56 % yield) as a yellow solid; δ_H (500 MHz, $CDCl_3$) 7.97-7.93 (m, 3 H, 2 Ar-H, 1 N*H*), 7.53 (d, *J* = 8.1 Hz, 1 H, Ar-H), 7.42-7.34 (m, 3 H, Ar-H), 7.24-7.21 (m, 1 H, Ar-H), 7.12 (d, *J* = 7.5 Hz, 2 H, Ar-H), 6.87 (td, *J* = 7.5, 0.9 Hz, 1 H, Ar-H), 2.30 (s, 3 H, CH_3); δ_C (125 MHz, $CDCl_3$) 141.2 (C), 134.5 (C), 130.5 (CH), 129.2 (CH), 128.4 (CH), 127.3 (CH), 126.4 (CH), 125.5 (C), 121.1 (C), 120.8 (CH), 113.3 (CH), 16.8 (CH_3); υ_{max}/cm^{-1} (neat) 3313, 1599, 1500

***N*-Phenyl-cyclopropanecarbohydrazonoyl chloride (298)[13]**

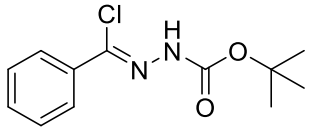


Following general procedure 4.8.1: *N'*-phenylcyclopropanehydrazide (1.0 g, 5.7 mmol) gave the product **70** (0.87 g, 79 % yield) as a pale-yellow solid; δ_H (500 MHz, $CDCl_3$) 7.55 (s, 1 H, N*H*), 7.26-7.23 (m, 2 H, Ar-H), 7.03-7.01 (m, 2 H, Ar-H), 6.87 (t, *J* = 7.3 Hz, 1 H, Ar-H), 1.99-1.94 (m, 1 H, CH), 1.01-0.98 (m, 1 H, CH_2), 0.87-0.83 (m, 2 H, CH_2); δ_C (125 MHz, $CDCl_3$) 143.9 (C), 129.2 (CH), 120.4 (CH), 112.9 (CH), 18.1 (CH), 6.4 (CH_2); υ_{max}/cm^{-1} (neat) 3315, 3050, 1599, 1497.

4.8.2. Chlorination of aryl hydrazones[23]

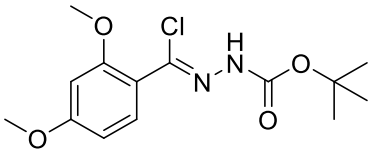
Aromatic aldehydes **311** (1.00 mmol) and tertbutylcarbazate/phenyl hydrazine (1.00 mmol) are placed in a 50 ml round bottomed flask where condensation between **311** and hydrazine derivative takes place instantaneously to form the carbo-tert-butoxyhydrazones **312**. In the case of solid aldehydes, 5.0 ml of methanol is required to add to the mixture and heated slightly on a water bath to furnish the condensation. Subsequently, *N*-chlorosuccinamide (1.00 mmol) is added to the dry DMF (10 ml) solution of compound **312** (1.00 mmol) at cold condition (temperature around 0 ^{o}C) and then stirred for 3 hour at room temperature. The progress of the reaction is monitored by TLC analysis. In cases of **313** and **314**, heating at 50 ^{o}C (overnight) was required to drive the reaction to completion. After completion of the reaction, the reaction mixture is poured into ice-cold water and the solid residue is filtered out, which is washed several times with distilled water, dried in open air and then crystallized from acetone.

***N*-(tert-butoxycarbonyl)-benzenecarbohydrazonyl chloride (313)**[23]



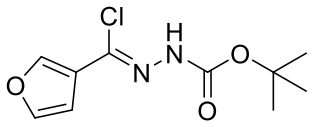
Following general procedure 4.8.2: *N*-(tert-butoxycarbonyl)-phenylhydrazone (2.0 g, 9.5 mmol) gave the product **70** (1.76 g, 73 % yield) as a white solid; δ_H (500 MHz, $CDCl_3$) 8.30 (s, 1 H, N*H*), 7.95 (app d, *J* = 8.0 Hz, 2 H, Ar-H), 7.44-7.39 (m, 3 H, Ar-H), 1.57 (s, 9 H, 3 x CH_3); δ_C (125 MHz, $CDCl_3$) 151.6 (C), 142. 1 (C), 133.4 (C), 130.5 (CH), 128.4 (CH), 127.4 (CH), 82.3 (C), 28.2 (CH_3); υ_{max}/cm^{-1} (neat) 3161, 2981, 1741, 1716, 1505

***N*-(tert-butoxycarbonyl)-2,4-dimethoxybenzenecarbohydrazonyl chloride (314)**



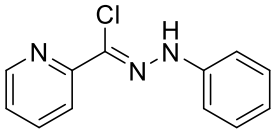
Following general procedure 4.8.2: *N*-(tert-butoxycarbonyl)-2,4-dimethoxyphenylhydrazone (3.0 g, 10.7 mmol) gave the product **70** (1.35 g, 40 % yield) as a white solid; δ_H (500 MHz, $CDCl_3$) 8.13-7.99 (m, 2 H, Ar-H), 7.83 (s, 1 H, N*H*), 6.44 (s, 1 H, Ar-H), 3.93 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 1.54 (s, 9 H, 3 x CH_3); δ_C (125 MHz, $CDCl_3$) 157.4 (C), 157.0 (C), 152.4 (C), 127.6 (CH), 115.8 (C), 115.1 (C), 95.9 (CH), 81.3 (C), 56.2 (OCH_3), 56.0 (OCH_3), 28.3 (CH_3); υ_{max}/cm^{-1} (neat) 3208, 2977, 1690, 1603, 1540

***N*-(tert-butoxycarbonyl)-furancarbohydrazonyl chloride (315)**



Following general procedure 4.8.2: *N*-(tert-butoxycarbonyl)-furanylhydrazone (2.0 g, 9.5 mmol) gave the product **70** (1.46 g, 63 % yield) as a pale yellow solid; δ_H (500 MHz, $CDCl_3$) 7.97 (s, 1 H, N*H*), 7.73 (s, 1 H, HetAr-H), 7.30 (app d, *J* = 1.8 Hz, 1 H, HetAr-H), 6.89 (s, 1 H, HetAr-H), 1.53 (s, 9 H, 3 x CH_3); δ_C (125 MHz, $CDCl_3$) 142.6 (CH), 137.4 (C), 134.7 (C), 116.6 (C), 109.8 (CH), 81.6 (C), 28.2 (CH_3); υ_{max}/cm^{-1} (neat) 3187, 2986, 1721, 1532

***N*-Phenyl-pyridyl-2-carbohydrazonoyl chloride (316)**

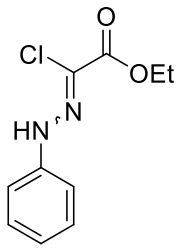


Following general procedure 4.8.2: *N*-phenyl-2-pyridylhydrazone (2.0 g, 10.1 mmol) gave the product **70** (2.79 g, 84 % yield) as a brown solid; δ_H (500 MHz, $CDCl_3$) 8.68-8.65 (m, 1 H, HetAr-H), 8.28 (s, 1 H, N*H*), 8.07 (d, *J* = 8.1 Hz, 1 H, HetAr-H), 7.76-7.71 (m, 1 H, HetAr-H), 7.33 (t, *J* = 7.5 Hz, 2 H, Ar-H), 7.28-7.25 (m, 1 H, HetAr-H), 7.21 (app d, *J* = 8.5 Hz, 2 H, Ar-H), 6.98 (t, *J* = 7.3 Hz, 1 H, Ar-H); δ_C (125 MHz, $CDCl_3$) 151.3 (C), 149.1 (CH), 142.8 (C), 136.3 (CH), 129.4 (CH), 125.2 (C), 123.4 (CH), 121.7 (CH), 121.1 (CH), 113.6 (CH); υ_{max}/cm^{-1} (neat) 3313, 1599, 1500

4.8.3 Japp-Klingemann synthesis[24]

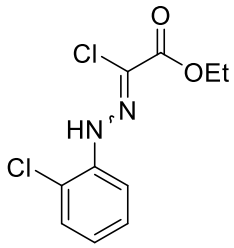
A solution of aniline derivative (20 mmol) in dilute HCl (1:1, 15 mL) was cooled to 0 °C, and a solution of $NaNO_2$ (1.1 equiv.) in H_2O (19 mL) was added drop wise over 10 min under vigorous stirring. The addition was controlled in such a way to keep the internal solution temperature at 0 °C. The resulting ice-cold solution of diazonium compound was added drop wise to a cold solution of ethyl-2-chloroacetoacetate (1.0 equiv.) and NaAOc (1.5 equiv.) in H_2O/EtOH (9:1, 111 mL). It is important to keep the diazonium solution at 0 °C during the addition. After complete addition, the mixture was stirred for 4 h, then poured into 150 mL of water, and the precipitate was filtered off. The crude was dried, furnishing the desired product.

Ethyl 2-chloro-2-(2-phenylhydrazono)acetate (321a)[19]



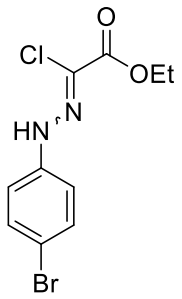
Following general procedure 4.8.3: Aniline (1.86 g, 20 mmol) and 2-chloro-3-oxobutanoate (3.29 g, 20 mmol) were reacted to afford the product **70** (4.12 g, 91 % yield) as a pale-brown solid; δ_H (500 MHz, $CDCl_3$) 8.30 (s, 1 H, N*H*), 7.30-7.27 (m, 2 H, Ar-H), 7.21-7.17 (m, 2 H, Ar-H), 7.01-6.98 (m, 1 H, Ar-H), 4.36-4.32 (m, 2 H, Ar-H), 1.35 (t, *J* = 7 Hz, 3 H, CH_3); δ_C (125 MHz, $CDCl_3$) 159.7 (C), 141.5 (C), 129.4 (CH), 123.1 (CH), 116.0 (C), 114.4 (CH), 62.7 (CH_2), 14.2 (CH_3); υ_{max}/cm^{-1} (neat) 3278, 2982, 1712, 1548

Ethyl 2-chloro-2-(2-(2-chlorophenyl)hydrazono)acetate (321b)[25]



Following general procedure 4.8.3: 2-chloroaniline (2.55 g, 20 mmol) and 2-chloro-3-oxobutanoate (3.29 g, 20 mmol) were reacted to afford the product **70** (4.54 g, 87 % yield) as a pale-yellow solid; δ_H (500 MHz, $CDCl_3$) 8.33 (s, 1 H, N*H*), 7.64 (dd, 8.2, 1.4 Hz, 1 H, Ar-H), 7.35 (dd, *J* = 7.9, 1.2 Hz, 1 H, Ar-H), 7.31-7.27 (m, 1 H, Ar-H), 6.98 (td, *J* = 7.9, 1.4 Hz, 1 H, Ar-H), 4.41 (q, *J* = 7.2 Hz, 2 H, CH_2), 1.42 (t, *J* = 7.2 Hz, 3 H, CH_3); δ_C (125 MHz, $CDCl_3$) 159.4 (C), 137.8 (C), 129.4 (CH), 128.1 (CH), 123.2 (CH), 119.1 (C), 118.5 (C), 115.7 (CH), 62.9 (CH_2), 14.2 (CH_3); υ_{max}/cm^{-1} (neat) 3312, 1720, 1557, 1504

Ethyl 2-chloro-2-(2-(4-bromophenyl)hydrazono)acetate (321c)[26]



Following general procedure 4.8.3: 4-bromoaniline (3.4 g, 20 mmol) and 2-chloro-3-oxobutanoate (3.29 g, 20 mmol) were reacted to afford the product **70** (5.79 g, 96 % yield) as a pale-yellow solid; δ_H (500 MHz, $CDCl_3$) 8.31 (s, 1 H, N*H*), 7.46-7.43 (m, 2 H, Ar-H), 7.14-7.10 (m, 2 H, Ar-H), 4.40 (q, *J* = 7.2 Hz, 2 H, CH_2), 1.41 (t, *J* = 7.2 Hz, 3 H, CH_3); δ_C (125 MHz, $CDCl_3$) 159.5 (C), 140.7 (C), 132.4 (CH), 116.9 (C), 116.0 (CH), 115.5 (C), 62.9 (CH_2), 14.2 (CH_3); υ_{max}/cm^{-1} (neat) 3248, 1705, 1554, 1508, 1483

4.9 Synthesis of 1,2,4-triazol-3-imine

4.9.1 Optimisation studies:

All optimization studies towards 1,2,4-triazole-3-imine were performed on 0.21 mmol of hydrazonyl chloride (**70**). The conversation rate for nitrile imine formation from **70** (Table 3.1) was calculated by GC-MS (dimer formation was observed at 11.58 min).

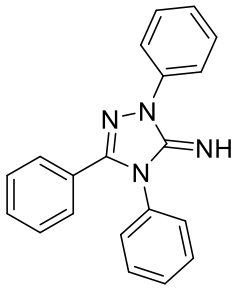
Where the ratio of **285**:**286** is mentioned (Table 3.2, 3.4, 3.5, 3.6), it is calculated from the crude NMR. A characteristic peak at 8.10 ppm (2 protons) is observed for **285**, whereas a peak at 8.20 ppm is representative for **286**. Where ratio of **285**:**286**:**284** is specified, it is calculated from the GC-MS spectra of the crude reaction mixture.

4.9.2 General procedure for the synthesis of 1,2,4-triazol-3-imine

In an oven dried 5 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 0.59 mmol) and *N*-aryl-*N*-tosyl cyanamide (1.25 equiv, 0.27 mmol) in anhydrous CH_3CN (0.5 M, 1 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18-crown-6 (2.75 equiv, 59 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, hydrazonoyl chloride (1 equiv, 0.21 mmol) was added which formed a paste like suspension. After 5 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction

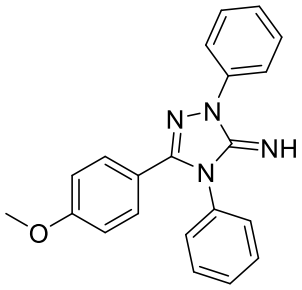
mixture was dissolved in 20 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with gradient elution of Pet Ether: EtOAc (9.5:0.5 to 1:1) followed by Pet Ether: EtOAc: NH_3 (1:1:0.1 to 0:1:0.2) to afford the 1,2,4-triazol-3-imine product.

2,4,5-Triphenyl-1*H*-1,2,4-triazol-3-imine (285)



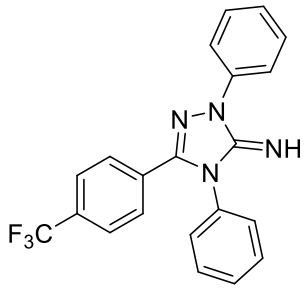
In an oven dried 5 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 90 mg, 0.59 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 74 mg, 0.27 mmol) in anhydrous CH_3CN (0.5 M, 1 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 157 mg, 59 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-Phenylbenzenecarbohydrazonoyl chloride **6a** (1 equiv, 50 mg, 0.21 mmol) was added which formed a paste like suspension. After 5 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 20 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with gradient elution of Pet Ether: EtOAc (9.5:0.5 to 1:1) followed by Pet Ether:EtOAc:NH_3 (1:1:0.1 to 0:1:0.2) to afford the product **1a** (60 mg, 89% yield) as a light brown solid, 89% yield; M. p. 182-183 °C; R_f 0.35 (0.2% NH_3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, J = 7.9 Hz, 2H, Ar-H), 7.54-7.46 (m, 5H, Ar-H), 7.39-7.34 (m, 3H, Ar-H), 7.32-7.22 (m, 5H, Ar-H), 5.16 (brs, 1H, N*H*) ppm; ^{13}C NMR (120 MHz, $CDCl_3$) : δ 153. 5 (C), 145.5 (C), 138.8 (C), 134.1 (C), 130.3 (CH), 130.0 (CH), 129.4 (CH), 129.0 (CH), 128.5 (CH), 128.3 (CH), 127.8 (CH), 126.3 (C), 124.9 (CH), 120.0 (CH) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3315, 3064, 2961, 1629, 1590, 1488, 1448, 1382, 1312, 1242; HRMS (ESI) calculated for $C_{20}H_{17}N_4$ $[M+H]^+$ 313. 1457 found 313.1446.

5-(4-methoxyphenyl)-4-phenyl-2-phenyl-2*H*-1,2,4-triazol-3(4*H*)-imine (322)



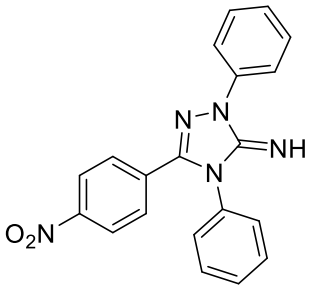
In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 160 mg, 1.05 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 130 mg, 0.48 mmol) in anhydrous CH_3CN (3 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 278 mg, 1.05 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-Phenyl-4-methoxybenzenecarbohydrazonoyl chloride **6b** (1 equiv, 100 mg, 0.38 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 20 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) followed by Pet Ether:EtOAc:NH_3 (6:4:0.05 to 3:7:0.05) to afford the product **2a** (112 mg, 86% yield) as a light orange-brown solid, 86% yield; M. p. 147-148 °C; R_f 0.39 (0.2% NH_3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, J = 7.8 Hz, 2H, Ar-H), 7.55-7.45 (m, 5H, Ar-H), 7.33-7.30 (m, 4H, Ar-H), 7.22 (t, J = 7.4 Hz, 1H, Ar-H), 6.81-6.78 (m, 2H, Ar-H), 4.72 (brs, 1H, NH), 3.79 (s, 3H, OCH_3) ppm ; ^{13}C NMR (125 MHz, $CDCl_3$) : δ 160.9 (C), 153. 6 (C), 145.4 (C), 139.0 (C), 134.2 (C), 130.2 (CH), 129.4(CH), 129.3 (CH), 128.9 (CH), 128.5 (CH), 124.7 (CH), 119.9 (CH), 118.7 (C), 113.9 (CH), 55.3 (OCH_3) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3327, 2930, 1634, 1609, 1595, 1500, 1432, 1307, 1253, 1022; HRMS (ESI) calculated for $C_{21}H_{19}N_4O$ $[M+H]^+$ 343.1553 found- 343.1552.

5-(4-trifluoromethylphenyl)-4-phenyl-2-phenyl-2*H*-1,2,4-triazol-3(4*H*)-imine



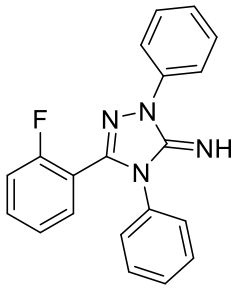
In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 140 mg, 0.92 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 113 mg, 0.42 mmol) in anhydrous CH_3CN (3 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 240 mg, 0.92 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-Phenyl-4-trifluoromethylbenzenecarbohydrazonoyl chloride **6b** (1 equiv, 100 mg, 0.33 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 20 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) followed by Pet Ether:EtOAc:NH_3 (6:4:0.05 to 3:7:0.05) to afford the product **2a** (103 mg, 81% yield) as a light brown solid. M. p. 144-146 °C R_f 0.61 (0.3% NH_3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): 8.12 (d, J = 8.1 Hz, 2H, Ar-H), 7.58-7.47 (m, 9H, Ar-H), 7.34-7.32 (m, 2H, Ar-H), 7.27-7.24 (m, 1H, Ar-H), 4.92 (brs, 1H, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) : δ 153. 4 (C), 144.1 (C), 138.7 (C), 133.8 (C), 131.7 (C, q, ^2J = 32.7 Hz), 130.5 (CH), 129.8 (CH), 129.0 (CH), 128.3 (CH), 128.0 (CH), 125.5 (CH, q, ^3J = 3.69 Hz), 125.2 (CH), 123.6 (C, d, ^1J = 272.48 Hz), 120.0 (CH) ppm; ^{19}F NMR (470.6 MHz, $CDCl_3$) δ -63.03 ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3312, 3063, 2921, 1652, 1617, 1595, 1491, 1429, 1390, 1324 (CF3 stretch), 1155, 1107; HRMS (ESI) calculated for $C_{21}H_{16}F_3N_4[M+H]^+$ 381.1322, found- 381.1329.

5-(4-nitrophenyl)-4-phenyl-2-phenyl-1*H*-1,2,4-triazol-3(4*H*)-imine (323)



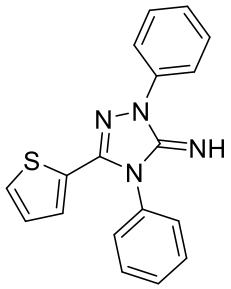
In an oven dried 25 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 450 mg, 2.99 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 370 mg, 1.36 mmol) in anhydrous CH_3CN (6 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 790 mg, 2.99 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-Phenyl-4-nitrobenzenecarbohydrazonoyl chloride **6b** (1 equiv, 300 mg, 1.09 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 35 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 8 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) followed by Pet Ether:EtOAc:NH_3 (6:4:0.05 to 1:9:0.1) to afford the product **2d** (296 mg, 76 % yield) as a bright yellow solid, 76 % yield; M. p. 201-203 °C; R_f 0.7 (0.2% NH_3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16-8.12 (m, 4H, Ar-H), 7.62-7.56 (m, 5H, Ar-H), 7.51 (t, J = 7.63 Hz, 2H, Ar-H), 7.36-7.34 (m, 2H, Ar-H), 7.28 (t, J = 7.32 Hz, 1H, Ar-H), 5.05 (brs, 1H, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) : δ 153. 3 (C), 148.2 (C), 143.4 (C), 138.5 (C), 133.7 (C), 132.2 (C), 130.7 (CH), 130.0 (CH), 129.1 (CH), 128.3 (CH), 128.2 (CH), 125.5 (CH), 123.7 (C), 120.1 (CH) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3318, 3058, 2935, 1641, 1593, 1548, 1491, 1455, 1337, 1235; HRMS (ESI) calculated for $C_{20}H_{16}N_5O_2[M+H]^+$ 358.1299, found 358.1298.

5-(2-fluorophenyl)-4-phenyl-2-phenyl-2*H*-1,2,4-triazol-3(4*H*)-imine (325)



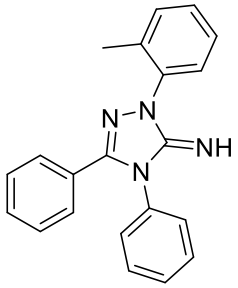
In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 168 mg, 1.10 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 136 mg, 0.50 mmol) in anhydrous CH_3CN (3 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 290 mg, 1.10 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-Phenyl-2-fluorobenzenecarbohydrazonoyl chloride **6b** (1 equiv, 100 mg, 0.40 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 25 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) followed by Pet Ether:EtOAc:NH_3 (6:4:0.05 to 2:8:0.05) to afford the product **2d** (132 mg, 81 % yield) as a grey solid, 81 % yield; M. p. 132-133 °C; R_f 0.55 (0.2% NH_3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 7.93 Hz, 2H, Ar-H), 7.52-7.37 (m, 7H, Ar-H), 7.26-7.16 (m, 4H, Ar-H), 6.97 (t, J = 9.0 Hz, 1H, Ar-H), 5.0 (brs, 1H, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) : δ 160.0 (C, d, J = 252.5 Hz), 152.9 (C), 142.4 (C), 138.8 (C), 133.6 (C), 132.5 (CH, d, J = 8.18 Hz), 131.2 (CH, d, J = 1.82 Hz), 129.8 (CH), 129.0 (CH, d, J = 2.72 Hz), 127.4 (CH), 125.0 (CH), 124.4 (CH, d, J = 3.63 Hz), 120.0 (CH), 116.1 (CH, d, J = 20.89 Hz), 115.0 (C, d, J = 14.53 Hz) ppm; ^{19}F NMR (470.6 MHz, $CDCl_3$) δ -110.53 ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3313, 3061, 2928, 1644, 1621, 1594, 1492, 1453, 1381, 1322, 1221, 1145; HRMS (ESI) calculated for $C_{20}H_{16}FN_4$ $[M+H]^+$ 331.1354, found 331.1359.

5-(thiophen-2-yl)-4-phenyl-2-phenyl-2*H*-1,2,4-triazol-3(4*H*)-imine (333)



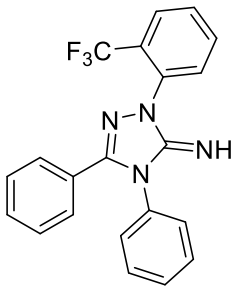
In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 176 mg, 1.16 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 143 mg, 0.53 mmol) in anhydrous CH_3CN (3 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 300 mg, 1.16 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-Phenyl-2-thiophenecarbohydrazonoyl chloride **6b** (1 equiv, 100 mg, 0.42 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 25 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) followed by Pet Ether:EtOAc:NH_3 (6:4:0.05 to 1:9:0.1) to afford the product **2d** (114 mg, 85 % yield) as a brown solid, 85 % yield; M. p. 146-147 °C; R_f 0.53 (0.2% NH_3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, J = 7.93 Hz, 2H, Ar-H), 7.63-7.58 (m, 3H, Ar-H), 7.49-7.42 (m, 4H, Ar-H), 7.33 (dd, J = 5.04 Hz, J = 1.07 Hz, 1H, Ar-H), 7.22 (t, J = 7.42 Hz, 1H, Ar-H), 6.90-6.89 (m, 1H, Ar-H), 6.75 (dd, J = 3.81 Hz, J = 1.07 Hz, 1H, Ar-H), 4.40 (brs, 1H, N*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) : δ 153. 5 (C), 141.3 (C), 138.8 (C), 133.4 (C), 130.5 (CH), 130.3 (CH), 129.3 (CH), 128.9 (CH), 128.0 (C), 127.9 (CH), 127.3 (CH), 124.9 (CH), 119.9 (CH) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3318, 3065, 2926, 1630, 1593, 1491, 1448, 1405, 1303, 1232; HRMS (ESI) calculated for $C_{18}H_{14}N_4NaS$ $[M+Na]^+$ 341.0831, found 341.0851.

2-(2-methylphenyl)-4-phenyl-5-phenyl-2*H*-1,2,4-triazol-3(4*H*)-imine (327)



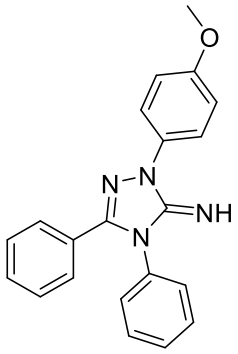
In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 170 mg, 1.12 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 139 mg, 0.51 mmol) in anhydrous CH_3CN (3 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 290 mg, 1.12 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-2-methylphenyl-3-phenylcarbohydrazonoyl chloride **6g** (1 equiv, 100 mg, 0.41 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 25 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) followed by Pet Ether:EtOAc:NH_3 (6:4:0.05 to 1:9:0.1) to afford the product **2d** (59 mg, 44 % yield) as a buff-coloured solid, 44 % yield; M. p. 145-146 °C; R_f 0.48 (0.2% NH_3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.41 (m, 4H, Ar-H), 7.36-7.32 (m, 8H, Ar-H), 7.27-7.24 (m, 2H, Ar-H), 4.48 (brs, 1H, NH), 2.41 (s, 3H, CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) : δ 154.5 (C), 145.9 (C), 136.2 (C), 136.1 (C), 134.9 (C), 131.5 (CH), 129.9 (CH), 129.8 (CH), 129.0 (CH), 128.8 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 127.0 (CH), 126.6 (C), 18.2 (CH_3) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3332, 3098, 2924, 1633, 1594, 1549, 1494, 1444, 1421, 1319; HRMS (ESI^+) calculated for $C_{21}H_{19}N_4$ $[M+H]^+$ 327.1604 found- 327.1633.

2-(2-trifluoromethylphenyl)-4-phenyl-5-phenyl-2*H*-1,2,4-triazol-3(4*H*)-imine (326)



In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 69 mg, 0.46 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 57 mg, 0.21 mmol) in anhydrous CH_3CN (1.5 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 121 mg, 0.46 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-2-trifluoromethylphenyl-3-phenylcarbohydrazonoyl chloride **6h** (1 equiv, 50 mg, 0.17 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 25 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) followed by Pet Ether:EtOAc:NH_3 (6:4:0.05 to 0:1:0.01) to afford the product **2h** (28 mg, 44 % yield) as a white solid, 44 % yield; M. p. 99-100 °C; R_f 0.33 (0.2% NH_3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7,.86 (d, J = 7.78 Hz, 1H, Ar-H), 7.75-7.70 (m, 2H, Ar-H), 7.60-7.57 (m, 1H, Ar-H), 7.51-7.43 (m, 3H, Ar-H), 7.36-7.33 (m, 5H, Ar-H), 7.28-7.25 (m, 2H, Ar-H), 3.99 (brs, 1H, N*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) : δ 155.1 (C), 146.2 (C), 135.3 (C), 134.5 (C), 133.1 (CH), 130.6 (CH), 130.0 (CH, d, J = 2.72 Hz), 129.2 (CH, d, J = 29.97 Hz), 128.8 (C, d, J = 31.8 Hz), 128.4 (CH), 128.1 (CH), 128.0 (CH, q, ^3J = 5.45 Hz), 127.8 (CH), 126.2 (C), 123.14 (C, d, ^1J = 274.29 Hz) ppm; ^{19}F NMR (470.6 MHz, $CDCl_3$) δ -60.26 ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3320, 3056, 1643, 1605, 1497, 1456, 1414, 1314, 1131; HRMS (ESI) calculated for $C_{21}H_{16}F_3N_4$ $[M+H]^+$ 381.1322, found 381. 1328.

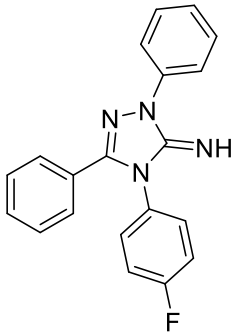
2-(4-methoxyphenyl)-4-phenyl-5-phenyl-2*H*-1,2,4-triazol-3(4*H*)-imine (328)



In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 80 mg, 0.53 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 65 mg, 0.24

mmol) in anhydrous CH_3CN (2.4 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 139 mg, 0.53 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-4-methoxyphenyl-3-phenylcarbohydrazonoyl chloride **6hi** (1 equiv, 50 mg, 0.19 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 20 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) followed by Pet Ether:EtOAc:NH_3 (1:1:0.02 to 0:1:0.01) to afford the product **2h** (54 mg, 83 % yield) as a white solid, 83 % yield; M. p. 164-165 °C; R_f 0.26 (0.2% NH_3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, J = 8.54 Hz, 2H, Ar-H), 7.52-7.45 (m, 3H, Ar-H), 7.37-7.25 (m, 7H, Ar-H), 7.0 (d, J = 8.7 Hz, 2H, Ar-H), 4.53 (brs, 1H, NH), 3.84 (s, 3H, OCH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) : δ 157.2 (C), 153. 7 (C), 145.3 (C), 134.3 (C), 132.0 (C), 130.2 (CH), 129.9 (CH), 129.2 (CH), 128.4 (CH), 128.3 (CH), 127.8 (CH), 126.4 (C), 122.4 (CH), 114.2 (CH), 55.5 (OCH_3) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3319, 2920, 2847, 1624, 1592, 1511, 1494, 1446, 1416, 1300, 1242, 1142; HRMS (ESI^+) calculated for $C_{21}H_{19}N_4O$ $[M+H]^+$ 343.1553 found 343.1557.

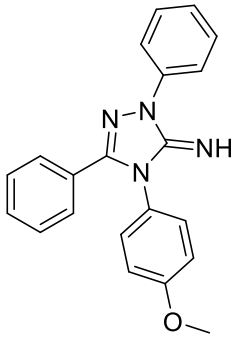
4-(4-fluorophenyl)-5-phenyl-2-phenyl-2*H*-1,2,4-triazol-3(4*H*)-imine (329)



In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 90 mg, 0.59 mmol) and *N*-(4-Fluorophenyl)-*N*-tosyl cyanamide **2c** (1.25 equiv, 82 mg, 0.27 mmol) in anhydrous CH_3CN (2.5 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 157 mg, 0.59 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-Phenylbenzenecarbohydrazonoyl chloride **6a** (1 equiv, 50 mg, 0.21 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile

components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 20 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) followed by Pet Ether:EtOAc:NH_3 (1:1:0.02 to 0:1:0.01) to afford the product **2j** (31 mg, 44 % yield) as a pale yellow solid, 44 % yield; M. p. 169-170 °C; R_f 0.24 (0.1% NH_3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J = 7.93 Hz, 2H, Ar-H), 7.48 (t, J = 8.24 Hz, 2H, Ar-H), 7.40-7.38 (m, 3H, Ar-H), 7.33-7.30 (m, 4H, Ar-H), 7.25-7.19 (m, 3H, Ar-H), 4.96 (brs, 1H, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.6 (C, d, J = 250.68 Hz), 153.5 (C), 145.5 (C), 138.7 (C), 130.3 (CH, d, J = 8.17 Hz), 130.1 (CH), 130.1 (C, d, J = 3.63 Hz), 129.1 (CH), 128.6 (CH), 127.8 (CH), 126.1 (C), 125.2 (CH), 120.1 (CH), 117.3 (CH, d, J = 23.61 Hz); ^{19}F NMR (470.6 MHz, $CDCl_3$) δ -110.54 ppm; IR: ῡ (cm^{-1}) 3312, 3065, 2928, 1645, 1594, 1504, 1411, 1322, 1218, 1143; HRMS (ESI$^+$) calculated for $C_{20}H_{16}FN_4$ $[M+H]^+$ 331.1354, found 331.1362.

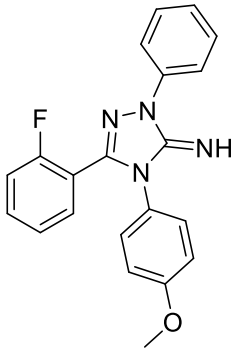
4-(4-methoxyphenyl)-5-phenyl-2-phenyl-2H-1,2,4-triazol-3(4*H*)-imine (330)



In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 90 mg, 0.59 mmol) and *N*-(4-methoxyphenyl)-*N*-tosyl cyanamide **2b** (1.25 equiv, 78 mg, 0.27 mmol) in anhydrous CH_3CN (2.5 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 157 mg, 0.59 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-Phenylbenzenecarbohydrazonoyl chloride **6a** (1 equiv, 50 mg, 0.21 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 20 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic

fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) followed by Pet Ether:EtOAc:NH_3 (1:1:0.02 to 0:1:0.01) to afford the product **2j** (45 mg, 61 % yield) as a light-brown solid, 61 % yield; M. p. 177-178 °C; R_f 0.51 (0.2% NH_3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J = 7.78 Hz, 2H, Ar-H), 7.47-7.34 (m, 5H, Ar-H), 7.30-7.19 (m, 5H, Ar-H), 7.01 (d, J = 8.7 Hz, 2H, Ar-H), 4.30 (brs, 1H, NH), 3.86 (s, 3H, OCH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1 (C), 153. 9 (C), 145.7 (C), 139.0 (C), 129.9 (CH), 129.7 (CH), 128.9 (CH), 128.4 (CH), 127.8 (CH), 126.4 (2 x C), 124.7 (CH), 119.8 (CH), 115.5 (CH), 55.5 (OCH_3) ppm; IR: ϑ (cm^{-1}) 3311, 2929, 1635, 1608, 1595, 1498, 1450, 1322, 1246; HRMS (ESI) calculated for $C_{21}H_{19}N_4O$ $[M+H]^+$ 343.1553, found 343.1564.

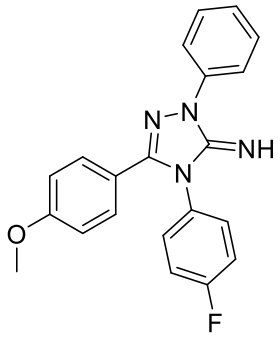
4-(4-methoxyphenyl)-5-(2-fluorophenyl)-2-phenyl-2*H*-1,2,4-triazol-3(4*H*)-imine (331)



In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 84 mg, 0.55 mmol) and *N*-(4-methoxypheny)l-*N*-tosyl cyanamide **2b** (1.25 equiv, 76 mg, 0.25 mmol) in anhydrous CH_3CN (2.5 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 146 mg, 0.55 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-Phenyl-2-fluorobenzenecarbohydrazonoyl chloride **6b** (1 equiv, 50 mg, 0.20 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 20 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) followed by Pet Ether:EtOAc:NH_3 (1:1:0.02 to 0:1:0.01) to afford the product **2l** (51 mg, 71 % yield) as a light-brown solid, 71 % yield; M. p. 149-150 °C; R_f 0.62 (0.1% NH_3 in EtOAc); ^{1}H NMR

(500 MHz, $CDCl_3$): δ 8.12 (d, J = 7.93 Hz, 2H, Ar-H), 7.52-7.45 (m, 1H, Ar-H) or dt, 7.23-7.16 (m, 4H, Ar-H), 7.0 (t, J = 9.15 Hz, 1H, Ar-H), 6.93 (d, J = 8.85 Hz, 2H, Ar-H), 4.98 (brs, 1H, NH), 3.82 (s, 3H, OCH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0 (C, d, J = 253.4 Hz), 159.8 (C), 153.4 (C), 142.7 (C), 138.9 (C), 132.4 (CH, d, J = 8.17 Hz), 131.3 (CH, d, J = 1.82 Hz), 128.9 (CH), 125.9 (C), 124.9 (CH), 124.4 (CH, d, J = 3.63 Hz), 119.8 (CH), 116.1 (CH, d, J = 20.89 Hz), 115.1 (C), 115.0 (CH), 55.4 (OCH_3) ppm; ^{19}F NMR (470.6 MHz, $CDCl_3$) δ -110.43 ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3305, 2962, 1647, 1623, 1591, 1490, 1457, 1384, 1321, 1224; HRMS (ESI^+) calculated for $C_{21}H_{18}FN_4O$ $[M+H]^+$ 361.1459, found 361.1468.

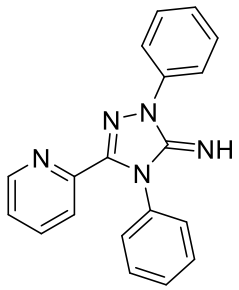
4-(4-fluorophenyl)-5-(4-methoxyphenyl)-2-phenyl-2*H*-1,2,4-triazol-3(4*H*)-imine (332)



In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 80 mg, 0.53 mmol) and *N*-(4-fluoropheny)l-*N*-tosyl cyanamide **2c** (1.25 equiv, 69 mg, 0.24 mmol) in anhydrous CH_3CN (2.5 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 139 mg, 0.53 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-Phenyl-4-methoxyphenylcarbohydrazonoyl chloride **6b** (1 equiv, 50 mg, 0.19 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 20 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) followed by Pet Ether:EtOAc:NH_3 (1:1:0.02 to 0:1:0.01) to afford the product **2l** (54 mg, 78 % yield) as a white fluffy solid, 78 % yield; M. p. 127-129 °C; R_f 0.66 (0.2% NH_3 in EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 7.93 Hz, 2H, Ar-H), 7.48 (t, J = 7.93 Hz, 2H, Ar-H), 7.33-7.30 (m, 4H, Ar-H), 7.22 (q, J = 7.93 Hz, 3H, Ar-H), 6.82 (d, J = 8.85 Hz, 2H, Ar-H), 4.64

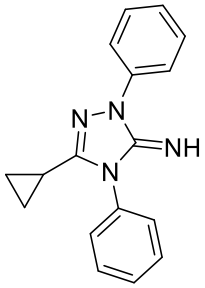
(brs, 1H, NH), 3.80 (s, 3H, OCH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.6 (C, d, J = 250.68 Hz), 160.9 (C), 153.5 (C), 145.4 (C), 138.8 (C), 130.4 (CH, d, J = 9.08 Hz), 130.2 (C, d, J = 2.72 Hz), 129.4 (CH), 129.0 (CH), 125.0 (CH), 120.1 (CH), 118.4 (C), 117.3 (CH, d, J = 22.71 Hz), 114.0 (CH), 55.3 (OCH_3) ppm; ^{19}F NMR (470.6 MHz, $CDCl_3$) δ -110.62 ppm; IR: ῡ (cm^{-1}) 3313, 2944, 1638, 1595, 1510, 1499, 1456, 1432, 1392, 1255, 1211; HRMS (ESI^+) calculated for $C_{21}H_{18}FN_4O$ $[M+H]^+$ 361.1459, found 361.1457.

5-pyridyl-4-phenyl-1-phenyl-2*H*-1,2,4-triazol-3(4*H*)-imine (334)



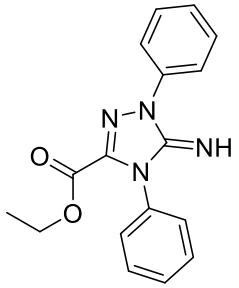
In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 360 mg, 2.37 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 293 mg, 1.08 mmol) in anhydrous CH_3CN (6.5 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 627 mg, 2.37 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-Phenyl-pyridylcarbohydrazonoyl chloride **6l** (1 equiv, 200 mg, 0.86 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 50 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 7 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 1:1) followed by EtOAc:NH_3 (1:0.02) to afford the product **2l** (190 mg, 70 % yield) as a buff-coloured solid, 70 % yield; M. p. 185-187 °C; R_f 0.69 (0.1% NH_3 in EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 8.36 (d, J = 4.27 Hz, 1H, Ar-H), 8.17 (d, J = 7.93 Hz, 2H, Ar-H), 7.82 (d, J = 7.93 Hz, 1H, Ar-H), 7.70 (t, J = 7.63 Hz, 1H, Ar-H), 7.51-7.46 (m, 5H, Ar-H), 7.36-7.31 (m, 2H, Ar-H), 7.24-7.21 (m, 2H, Ar-H), 5.01 (brs, 1H, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.8 (C), 149.1 (CH), 146.0 (C), 144.4 (C), 138.8 (C), 136.4 (CH), 134.6 (C), 129.7 (CH), 128.9 (CH), 128.2 (CH), 125.0 (CH), 124.1 (CH), 123.0 (CH), 120.0 (CH) ppm; IR: ῡ (cm^{-1}) 3318, 3057, 2921, 1633, 1586, 1489, 1477, 1389, 1242; HRMS (ESI^+) calculated for $C_{19}H_{16}N_5$ $[M+H]^+$ 314.1400, found 314.1402.

5-cyclopropyl-4-phenyl-1-phenyl-2*H*-1,2,4-triazol-3(4*H*)-imine (335)



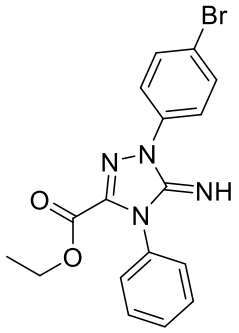
In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 600 mg, 3.95 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2c** (1.25 equiv, 495 mg, 1.80 mmol) in anhydrous CH_3CN (8 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 1.04 g, 3.95 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-Phenyl-cyclopropanecarbohydrazonoyl chloride **6b** (1 equiv, 280 mg, 1.44 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 50 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 8 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) followed by Pet Ether:EtOAc:NH_3 (1:1:0.02 to 0:1:0.01) to afford the product **2l** (230 mg, 58 % yield) as a brown solid, 58 % yield; M. p. 110-111 °C; R_f 0.27 (0.2% NH_3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, J = 7.93 Hz, 2H, Ar-H), 7.61-7.58 (m, 2H, Ar-H), 7.53-7.50 (m, 1H, Ar-H), 7.46-7.41 (m, 4H, Ar-H), 7.17 (t, J = 7.4 Hz, 1H, Ar-H), 4.63 (brs, 1H, NH), 1.45-1.40 (m, 1H, CH-cyclopropyl), 1.15-1.06 (m, 2H, CH_2), 0.94-0.84 (m, 2H, CH_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.3 (C), 148.7 (C), 139.0 (C), 133.1 (C), 130.2 (CH), 129.3 (CH), 128.9 (CH), 128.2 (CH), 124.4 (CH), 119.6 (CH), 7.22 (CH_2), 6.42 (CH) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3327, 3047, 1638, 1593, 1495, 1457, 1410, 1230; HRMS (ESI^+) calculated for $C_{17}H_{17}N_4$ $[M+H]^+$ 277.1448, found 277.1460.

3-imino-2,4-diphenyl-2H-1,2,4-triazole-5(4*H*)-carboxylic acid ethyl ester (337)



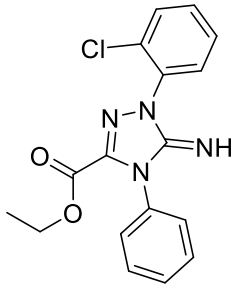
In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 92 mg, 0.60 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 75 mg, 0.27 mmol) in anhydrous CH_3CN (1.5 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 160 mg, 0.60 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, C-ethoxycarbonyl-*N*-phenylhydrazonoyl chloride **6b** (1 equiv, 50 mg, 0.22 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 20 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9.5:0.5 to 1:9) to afford the product **2l** (55 mg, 81 % yield) as a light brown solid, 81 % yield; M. p. 130-132 °C; R_f 0.44 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 7.93 Hz, 2H, Ar-H), 7.59-7.53 (m, 3H, Ar-H), 7.48 (t, J = 7.85 Hz, 1H, Ar-H), 7.36 (d, J = 7.17 Hz, 1H, Ar-H), 7.30-7.27 (m, 1H, Ar-H), 4.29 (q, J = 7.12 Hz, 2H, CH_2), 4.00 (brs, 1H, NH), 1.26-1.23 (m, 3H, CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3 (C), 153.4 (C), 138.0 (C), 136.9 (C), 133.6 (C), 129.9 (CH), 129.7 (CH), 129.0 (CH), 128.1 (CH), 126.2 (CH), 120.9 (CH), 62.4 (CH_2), 13.8 (CH_3) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3305, 3274, 3049, 2983, 1738, 1634, 1595, 1492, 1435, 1391, 1310, 1208; HRMS (ESI^+) calculated for $C_{17}H_{17}N_4O_2$ $[M+H]^+$ 309.1346, found 309.1340.

3-imino-2-(4-bromophenyl)-4-phenyl-2*H*-1,2,4-triazole-5(4*H*)-carboxylic acid ethyl ester (338)



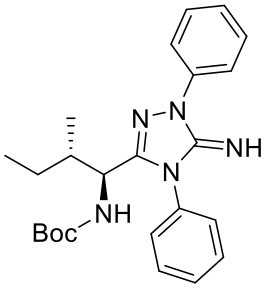
In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 136 mg, 0.90 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 111 mg, 0.41 mmol) in anhydrous CH_3CN (2.5 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 238 mg, 0.90 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, C-ethoxycarbonyl-*N*-(4-bromophenyl)hydrazonoyl chloride **6b** (1 equiv, 100 mg, 0.33 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 20 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) to afford the product **2l** (90 mg, 71 % yield) as a Pale-yellow solid, 71 % yield; M. p. 194-195 °C; R_f 0.36 (1:1 Pet Ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, J = 8.09 Hz, 2H, Ar-H), 7.59-7.53 (m, 5H, Ar-H), 7.34 (d, J = 6.71 Hz, 2H, Ar-H), 5.10 (brs, 1H, NH), 4.28 (q, J = 7.12 Hz, 2H, CH_2), 1.24 (t, J = 7.12 Hz, 3H, CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2 (C), 153.0 (C), 137.4 (C), 137.0 (C), 133.4 (C), 131.9 (CH), 130.0 (CH), 129.9 (CH), 128.1 (CH), 121.6 (CH), 118.8 (C), 62.4 (CH_2), 13.8 (CH_3) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3310, 3099, 2977, 1726, 1645, 1588, 1552, 1489, 1447, 1387, 1209; HRMS (ESI^+) calculated for $C_{17}H_{16}BrN_4O_2$ $[M+H]^+$ 387.0451, found 387.0448.

3-imino-2-(2-chlorophenyl)-4-phenyl-2*H*-1,2,4-triazole-5(4*H*)-carboxylic acid ethyl ester (339)



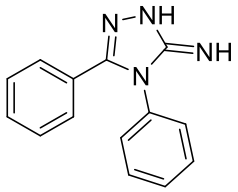
In an oven dried 25 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 480 mg, 3.16 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 390 mg, 1.43 mmol) in anhydrous CH_3CN (6 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 850 mg, 3.16 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, C-ethoxycarbonyl-*N*-(2-chlorophenyl) hydrazonoyl chloride **6b** (1 equiv, 300 mg, 1.15 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 35 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 8 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 1:1) to afford the product **2l** (230 mg, 60 % yield) as a pale yellow-orange solid, 60 % yield; M. p. 126-128 °C; R_f 0.42 (0.2% NH_3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62-7.50 (m, 5H, Ar-H), 7.44-7.40 (m, 4H, Ar-H), 4.66 (brs, 1H, NH), 4.29 (q, J = 7.09 Hz, 2H, CH_2), 1.25 (t, J = 7.09 Hz, 3H, CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3 (C), 153.8 (C), 137.8 (C), 134.2 (C), 134.0 (C), 132.8 (C), 130.8 (CH), 130.1 (CH), 129.7 (CH), 129.5 (CH), 127.9 (CH), 62.4 (CH_2), 13.9 (CH_3) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3331, 3039, 2980, 1732, 1646, 1588, 1542, 1486, 1443, 1380, 1200; HRMS (ESI^+) calculated for $C_{17}H_{16}ClN_4O_2$ $[M+H]^+$ 343.0956, found 343.0961.

5-(1-tert-butoxycarbonylamino-2-methyl-butyl)-2,4-diphenyl-2*H*-1,2,4-triazol-3(4*H*)-imine (340)



In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 61 mg, 0.40 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 50 mg, 0.18 mmol) in anhydrous CH_3CN (1 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 107 mg, 0.40 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-Phenyl-3-(1-tert-butoxycarbonyl-amino)-2-butylpropanecarbohydrazonoyl chloride **6b** (1 equiv, 50 mg, 0.15 mmol in 1.5 ml CH_3CN) was added dropwise over a period of 5 minutes which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 20 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 4 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 7:3) followed by Pet Ether:EtOAc:NH_3 (1:1:0.02 to 0:1:0.01) to afford the product **2l** (37 mg, 61 % yield) as a dark-brown solid, 61 % yield; M. p. 61-62 °C; R_f 0.62 (0.2% NH_3 in EtOAc); $[\alpha]_D$ – 41.55°; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, J = 7.93 Hz, 2H, Ar-H), 7.60-7.57 (m, 2H, Ar-H), 7.54-7.51 (m, 1H, Ar-H), 7.45-7.40 (m, 4H, Ar-H), 7.19 (t, J = 7.24 Hz, 1H, Ar-H), 4.99 (d, J = 9.31 Hz, 1H, NH{-boc}), 4.46 (t, J = 8.24 Hz, CH), 1.71-1.59 (m, 1H, CH), 1.53-1.43 (m, 9H, 3xCH_3 & 1H, CH_2), 1.09-0.98 (m, 1H, CH_2), 0.86 (m, 6H, 2xCH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.1 (C), 153.2 (C), 147.4 (C), 138.8 (C), 132.5 (C), 130.4 (CH), 129.8 (CH), 128.9 (CH), 128.5 (CH), 124.8 (CH), 119.8 (CH), 79.9 (C), 51.0 (CH), 38.3 (CH), 28.3 (CH_3), 24.2 (CH_2), 15.7 (CH), 11.3 (CH) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3317, 2967, 2928, 1706, 1637, 1596, 1495, 1455, 1365, 1231, 1161; HRMS (ESI^+) calculated for $C_{24}H_{32}N_5O_2$ $[M+H]^+$ 422.2551, found 422.2577.

4,5-diphenyl-2*H*-1,2,4-triazol-3(4*H*)-imine (336)



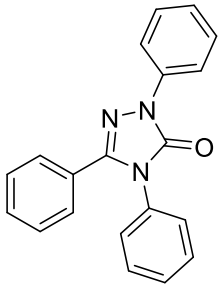
In an oven dried 10 mL round bottom flask cooled under nitrogen atmosphere, was taken CsF (2.75 equiv, 328 mg, 2.16 mmol) and *N*-phenyl-*N*-tosyl cyanamide **2a** (1.25 equiv, 267 mg, 0.98 mmol) in anhydrous CH_3CN (6 mL). The reaction mixture was introduced to an ice-bath, followed by addition of 18C6 (2.75 equiv, 570 mg, 2.16 mmol) in a single portion under vigorous stirring conditions. After 10 minutes, *N*-(tert-butoxycarbonylamino)-phenylhydrazonoyl chloride **6b** (1 equiv, 200 mg, 0.78 mmol) was added which turned the reaction mixture into a paste like suspension. After 10 min, the flask was removed from the ice-bath, and the volatile components were removed under vacuum. The organic residue from the reaction mixture was dissolved in 50 mL ethyl acetate, and washed with sat. aqueous KCl (3 x 8 mL). The organic fraction was dried over anhydrous Na_2SO_4 and solvents removed under reduced pressure. The purification was carried out using a short column packed with silica gel (7 cm height) with a gradient elution of Pet Ether: EtOAc (9:1 to 1:9) followed by EtOAc:CH_3CN:NH_3 (9:1:0.2 to 7:3:0.5) to afford the product **2l** (114 mg, 62 % yield) as a white crystalline solid, 62 % yield; M. p. 226-228 °C; R_f 0.2 (0.2% NH_3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55-7.50 (m, 3H, Ar-H), 7.38-7.36 (m, 2H, Ar-H), 7.31-7.23 (m, 5H, Ar-H), 4.51 (brs, 2H, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7 (C), 150.1 (C), 134.0 (C), 130.4 (CH), 129.8 (CH), 129.1 (CH), 128.4 (CH), 127.7 (CH), 127.3 (CH), 127.3 (C) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3427, 3058, 1639, 1594, 1562, 1497, 1484, 1355; HRMS (ESI^+) calculated for $C_{14}H_{13}N_4$ $[M+H]^+$ 237.1135, found 237.1144.

4.10 Synthesis of 1,2,4-triazol-3-one[27]

1,2,4-triazol-3-imine (0.16 mmol) and sodium acetate (3.2 mmol) were taken in a 10 mL oven dried round bottom flask and dissolved in 2.6 mL 50% acetic acid solution. At 0-5 °C, sodium nitrite (4.00 mmol) was added portion-wise over a period of 3 minutes. After complete addition, the reaction mixture was allowed to stir at room temperature. After 6 hours, the reaction mixture was boiled for 10 minutes to expel the nitrous gases (visible as yellow fumes). The reaction mixture was then neutralised with sat. aqueous $NaHCO_3$ and extracted with ethyl acetate (20 mL). The ethyl acetate fraction was separated, washed with brine (10 mL) and dried

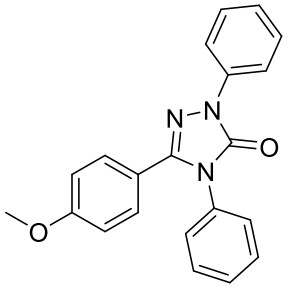
over anhydrous Na_2SO_4. The volatile components were then removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether: EtOAc (8:2) to afford 1,2,4-triazol-3-one products.

2,4,5-triphenyl-2*H*-1,2,4-triazol-3(4*H*)-one (345)[28]



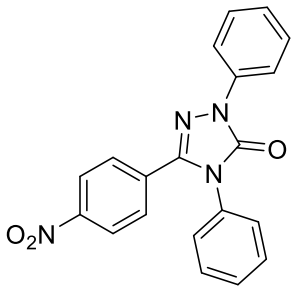
1,3,4-Triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-imine (50 mg, 0.16 mmol) and sodium acetate (262 mg, 3.2 mmol) were taken in a 10 mL oven dried round bottom flask and dissolved in 2.6 mL 50% acetic acid solution. At 0-5 °C, sodium nitrite (276 mg, 4.00 mmol) was added portion-wise over a period of 3 minutes. After complete addition, the reaction mixture was allowed to stir at room temperature. After 6 hours, the reaction mixture was boiled for 10 minutes to expel the nitrous gases (visible as yellow fumes). The reaction mixture was then neutralized with sat. (aq) $NaHCO_3$ and extracted with ethyl acetate (20 mL). The ethyl acetate fraction was separated, washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The volatile components were then removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether:EtOAc (8:2) to afford the product **4a** (38 mg, 76% yield) as a white solid, 76% yield; M. p. 214-215 °C [lit. 213-214][5]; R_f 0.46 (4:1 Pet Ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J = 8.09 Hz, 2H, Ar-H), 7.50-7.40 (m, 8H, Ar-H), 7.35-7.31 (m, 4H, Ar-H), 7.28-7.25 (m, 1H, Ar-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.8 (C), 145.2 (C), 137.8 (C), 133.5 (C), 130.3 (CH), 129.5 (CH), 129.0 (CH), 128.8 (CH), 128.6 (CH), 128.0 (CH), 127.3 (CH), 126.4 (C), 125.5 (CH), 118.9 (CH); IR: ϑ (cm^{-1}) 2920, 2852, 1700, 1574, 1490, 1373; HRMS (ESI^+) calculated for $C_{20}H_{16}N_3O$ $[M+H]^+$ 314.1288, found 314.1297.

5-(4-Methoxyphenyl)-4-phenyl-2-phenyl-2*H*-1,2,4-triazol-3(4*H*)-one (347)[29]



3-(4-methoxyphenyl)-1,4-diphenyl-1*H*-1,2,4-triazol-5-imine (100 mg, 0.29 mmol) and sodium acetate (480mg, 5.84 mmol) were taken in a 25 mL oven dried round bottom flask and dissolved in 5 mL 50% acetic acid solution. At 0-5 ^{o}C, sodium nitrite (500 mg, 7.3 mmol) was added portion-wise over a period of 3 minutes. After complete addition, the reaction mixture was allowed to stir at room temperature. After 4 hours, the reaction mixture was boiled for 10 minutes to expel the nitrous gases (visible as yellow fumes). The reaction mixture was then neutralized with sat. (aq) $NaHCO_3$ and extracted with ethyl acetate (30 mL). The ethyl acetate fraction was separated, washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The volatile components were then removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether:EtOAc (8:2) to afford the product **4a** (84 mg, 84 % yield) as a white solid, 84 % yield; M. p. 178-179 °C [lit. 173-174 °C]; R_f 0.32 (4:1 Pet Ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, J = 7.63 Hz, 2H, Ar-H), 7.47-7.40 (m, 5H, Ar-H), 7.34 (d, J = 8.85 Hz, 2H, Ar-H), 7.30 (d, J = 6.87 Hz, 2H, Ar-H), 7.25-7.22 (m, 1H, Ar-h), 6.82 (d, J = 9.0 Hz, 2H, Ar-H), 3.79 (s, 3H, OCH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0 (C), 151.8 (C), 145.1 (C), 137.9 (C), 133.6 (C), 129.5 (CH), 129.5 (CH), 128.9 (CH), 128.8 (CH), 127.4 (CH), 125.3 (CH), 118.8 (CH), 118.6 (C), 114.0 (CH), 55.3 (OCH_3) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 2928, 1701, 1597, 1511, 1493, 1373, 1255; HRMS (ESI) calculated for $C_{21}H_{18}N_3O_2$ $[M+H]^+$ 344.1394, found 344.1395.

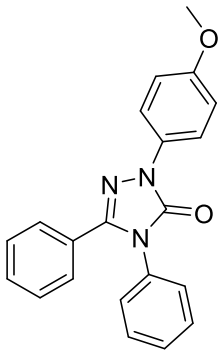
5-(4-nitrophenyl)-4-phenyyl-2-phenyl-*2H-1*,2,4-triazol-3(4*H*)-one (346)[30]



3-(4-nitrophenyl)-1,4-diphenyl-1*H*-1,2,4-triazol-5-imine (150 mg, 0.42 mmol) and sodium acetate (688 mg, 5.84 mmol) were taken in a 25 mL oven dried round bottom flask and

dissolved in 7 mL 50% acetic acid solution. At 0-5 °C, sodium nitrite (720 mg, 10.5 mmol) was added portion-wise over a period of 5 minutes. After complete addition, the reaction mixture was allowed to stir at room temperature. After 4 hours, the reaction mixture was boiled for 10 minutes to expel the nitrous gases (visible as yellow fumes). The reaction mixture was then neutralized with sat. (aq) $NaHCO_3$ and extracted with ethyl acetate (35 mL). The ethyl acetate fraction was separated, washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The volatile components were then removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether:EtOAc (8:2) to afford the product **4a** (133 mg, 89 % yield) as a yellow solid, 89 % yield; M. p. 199-201 °C; R_f 0.35 (4:1 Pet Ether:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, J = 8.85 Hz, 2H, Ar-H), 8.12 (d, J = 7.78 Hz, 2H, Ar-H), 7.63 (d, J = 9.0 Hz, 2H, Ar-H), 7.55-7.48 (m, 5H, Ar-H), 7.33-7.29 (m, 3H, Ar-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.6 (C), 148.5 (C), 143.0 (C), 137.5 (C), 133.0 (C), 132.3 (C), 130.0 (CH), 129.5 (CH), 129.1 (CH), 128.6 (CH), 127.3 (CH), 126.1 (CH), 123.8 (CH), 119.0 (CH); IR: $\tilde{\upsilon}$ (cm^{-1}) 1713, 1594, 1547, 1510, 1494, 1342; HRMS (ESI) calculated for $C_{20}H_{14}N_4NaO_3$ $[M+Na]^+$ 381.0958, found 381.0949.

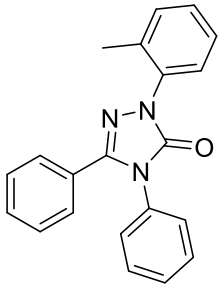
2-(4-Methoxyphenyl)-5-phenyl-4-phenyl-2*H*-1,2,4-triazol-3(4*H*)-one (350)



1-(4-methoxyphenyl)-3,4-diphenyl-1*H*-1,2,4-triazol-5-imine (78 mg, 0.23 mmol) and sodium acetate (370 mg, 4.55 mmol) were taken in a 25 mL oven dried round bottom flask and dissolved in 3.8 mL 50% acetic acid solution. At 0-5 °C, sodium nitrite (390 mg, 5.69 mmol) was added portion-wise over a period of 5 minutes. After complete addition, the reaction mixture was allowed to stir at room temperature. After 4 hours, the reaction mixture was boiled for 10 minutes to expel the nitrous gases (visible as yellow fumes). The reaction mixture was then neutralized with sat. (aq) $NaHCO_3$ and extracted with ethyl acetate (25 mL). The ethyl acetate fraction was separated, washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The volatile components were then removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether:EtOAc (8:2) to afford the product **4a** (57 mg,

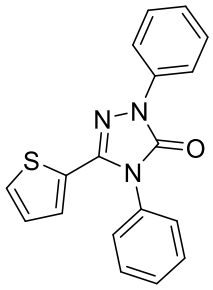
73 % yield) as a white solid, 73 % yield; M. p. 198-199 °C; R_f 0.32 (4:1 Pet Ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): 8.01 (d, J = 8.85 Hz, 2H, Ar-H), 7.47-7.39 (m, 6H, Ar-H), 7.34-7.30 (m, 4H, Ar-H), 7.00 (d, J = 8.85 Hz, 2H, Ar-H), 3.85 (s, 3H, OCH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.4 (C), 151.7 (C), 144.8 (C), 133.5 (C), 131.2 (C), 130.2 (CH), 129.5 (CH), 128.7 (CH), 128.5 (CH), 128.0 (CH), 127.3 (CH), 126.4 (C), 120.7 (CH), 114.1 (CH), 55.5 (OCH_3) ppm; IR: ῡ (cm^{-1}) 3047, 2920, 2849, 1695, 1593, 1512, 1498, 1448, 1379, 1254; HRMS (ESI) calculated for $C_{21}H_{18}N_3O_2$ $[M+H]^+$ 344.1394, found 344.1391.

2-(2-Methylphenyl)-5-phenyl-4-phenyl-2*H*-1,2,4-triazol-3(4*H*)-one (349)



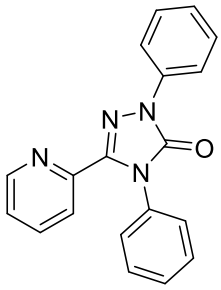
1-(4-methoxyphenyl)-3,4-diphenyl-1*H*-1,2,4-triazol-5-imine (88 mg, 0.27 mmol) and sodium acetate (440 mg, 5.39 mmol) were taken in a 25 mL oven dried round bottom flask and dissolved in 4.5 mL 50% acetic acid solution. At 0-5 ^{o}C, sodium nitrite (460 mg, 6.74 mmol) was added portion-wise over a period of 5 minutes. After complete addition, the reaction mixture was allowed to stir at room temperature. After 6 hours, the reaction mixture was boiled for 10 minutes to expel the nitrous gases (visible as yellow fumes). The reaction mixture was then neutralized with sat. (aq) $NaHCO_3$ and extracted with ethyl acetate (25 mL). The ethyl acetate fraction was separated, washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The volatile components were then removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1 to 7:3) to afford the product **4a** (72 mg, 82 % yield) as a white solid, 82 % yield; M. p. 145-146 °C; R_f 0.28 (4:1 Pet Ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.52 (m, 1H, Ar-H), 7.48-7.39 (m, 6H, Ar-H), 7.35-7.31 (m, 7H, Ar-H), 2.45 (s, 3H, CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.4 (C), 145.4 (C), 135.5 (C), 135.2 (C), 133.7 (C), 131.2 (CH), 130.1 (CH), 129.5 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 127.9 (CH), 127.2 (CH), 127.0 (CH), 126.6 (CH), 126.5 (C), 18.4 (CH_3) ppm; IR: ῡ (cm^{-1}) 3051, 1710, 1590, 1493, 1444, 1409, 1366, 1320; HRMS (ESI) calculated for $C_{21}H_{18}N_3O$ $[M+H]^+$ 328.1444, found 328.1451.

5-(thiophen-2-yl)-5-phenyl-4-phenyl-2*H*-1,2,4-triazol-3(4*H*)-one (351)



3-(thiophen-2-yl)-1,4-diphenyl-1*H*-1,2,4-triazol-5-imine (150 mg, 0.47 mmol) and sodium acetate (770 mg, 9.42 mmol) were taken in a 25 mL oven dried round bottom flask and dissolved in 8 mL 50% acetic acid solution. At 0-5 ^{o}C, sodium nitrite (812 mg, 11.78 mmol) was added portion-wise over a period of 5 minutes. After complete addition, the reaction mixture was allowed to stir at room temperature. After 6 hours, the reaction mixture was boiled for 10 minutes to expel the nitrous gases (visible as yellow fumes). The reaction mixture was then neutralized with sat. (aq) $NaHCO_3$ and extracted with ethyl acetate (35 mL). The ethyl acetate fraction was separated, washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The volatile components were then removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1 to 7:3) to afford the product **4a** (125 mg, 88 % yield) as a white solid, 88 % yield; M. p. 196-197 °C; R_f 0.39 (4:1 Pet ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 8.09 Hz, 2H, Ar-H), 7.54-7.53 (m, 3H, Ar-H), 7.46 (t, J = 7.85 Hz, 2H, Ar-H), 7.42-7.40 (m, 2H, Ar-H), 7.36 (d, J = 4.88 Hz, 1H, HetAr-H), 7.26-7.23 (m, 1H, Ar-h), 6.91 (t, J = 4.35 Hz, 1H, HetAr-H), 6.81 (d, J = 3.36 Hz, 1H, HetAr-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.7 (C), 141.0 (C), 137.7 (C), 132.9 (C), 129.8 (CH), 129.0 (CH), 128.4 (CH), 128.3 (CH), 127.9 (C), 127.4 (CH), 125.5 (CH), 118.8 (CH) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3102, 2046, 1698, 1591, 1491, 1453, 1374, 1303; HRMS (ESI) calculated for $C_{18}H_{14}N_3OS$ $[M+H]^+$ 320.0852, found 320.0850.

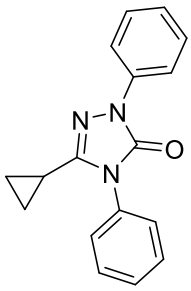
5-Pyridyl-5-phenyl-4-phenyl-2*H*-1,2,4-triazol-3(4*H*)-one (352)



3-pyridyl-1,4-diphenyl-1*H*-1,2,4-triazol-5-imine (140 mg, 0.45 mmol) and sodium acetate (730 mg, 8.94 mmol) were taken in a 25 mL oven dried round bottom flask and dissolved in 7.3 mL 50% acetic acid solution. At 0-5 ^{o}C, sodium nitrite (770 mg, 11.18 mmol) was added

portion-wise over a period of 5 minutes. After complete addition, the reaction mixture was allowed to stir at room temperature. After 6 hours, the reaction mixture was boiled for 10 minutes to expel the nitrous gases (visible as yellow fumes). The reaction mixture was then neutralized with sat. (aq) $NaHCO_3$ and extracted with ethyl acetate (35 mL). The ethyl acetate fraction was separated, washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The volatile components were then removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1 to 7:3) to afford the product **4a** (110 mg, 79 % yield) as a pale-yellow solid, 79 % yield; M. p. 205-206 °C; R_f 0.25 (4:1 Pet ether:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (d, J = 4.12 Hz, 1H, HetAr-H), 8.06 (d, J = 8.09 Hz, 2H, Ar-H), 7.72-7.65 (m, 2H, HetAr-H), 7.41-7.31 (m, 5H, Ar-H), 7.24-7.17 (m, 4H, Ar-H and HetAr-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.9 (C), 149.4 (CH), 146.1 (C), 144.1 (C), 137.7 (C), 136.6 (CH), 134.0 (C), 129.0 (CH), 129.0 (CH), 128.4 (CH), 127.2 (C), 125.7 (CH), 124.4 (CH), 123.3 (CH), 119.0 (CH) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3050, 2927, 1703, 1595, 1489, 1452, 1372, 1157; HRMS (ESI) calculated for $C_{19}H_{15}N_4O$ $[M+H]^+$ 315.1240, found 315.1244.

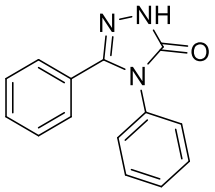
5-(cyclopropyl)-5-phenyl-4-phenyl-2*H*-1,2,4-triazol-3(4*H*)-one (353)



3-cyclopropyl-1,4-diphenyl-1*H*-1,2,4-triazol-5-imine (120 mg, 0.43 mmol) and sodium acetate (712 mg, 8.68 mmol) were taken in a 25 mL oven dried round bottom flask and dissolved in 7.2 mL 50% acetic acid solution. At 0-5 °C, sodium nitrite (748 mg, 10.85 mmol) was added portion-wise over a period of 5 minutes. After complete addition, the reaction mixture was allowed to stir at room temperature. After 6 hours, the reaction mixture was boiled for 10 minutes to expel the nitrous gases (visible as yellow fumes). The reaction mixture was then neutralized with sat. (aq) $NaHCO_3$ and extracted with ethyl acetate (35 mL). The ethyl acetate fraction was separated, washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The volatile components were then removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1) to afford the product **4a** (87 mg, 73 % yield) as a light-orange solid, 73 % yield; M. p. 91-92 °C; R_f 0.43 (4:1 Pet ether: EtOAc);

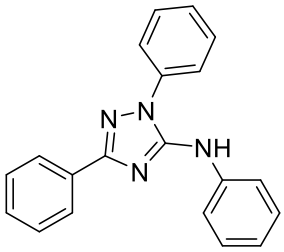
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, J = 7.78 Hz, 2H, Ar-H), 7.57-7.41 (m, 7H, Ar-H), 7.21 (t, J = 7.4 Hz, 1H, Ar-H), 1.62-1.56 (m, 1H, cyclopropyl-H), 1.20-1.17 (m, 2H, cyclopropyl-H), 0.99-0.96 (m, 2H, cyclopropyl-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.6 (C), 148.3 (C), 138.0 (C), 132.8 (C), 129.6 (CH), 128.9 (CH), 128.8 (CH), 127.1 (CH), 125.1 (CH), 118.6 (CH), 7.54 (CH_2), 6.85 (CH) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3018, 1709, 1594, 1577, 1492, 1463, 1375, 1261; HRMS (ESI) calculated for $C_{17}H_{16}N_3O$ $[M+H]^+$ 278.1288, found 278.1293.

4,5-Diphenyl-2*H*-1,2,4-triazol-3(4*H*)-one (354)



3,4-diphenyl-1*H*-1,2,4-triazol-5-imine (50 mg, 0.21 mmol) and sodium acetate (347 mg, 4.23 mmol) were taken in a 10 mL oven dried round bottom flask and dissolved in 3.5 mL 50% acetic acid solution. At 0-5 ^{o}C, sodium nitrite (365 mg, 5.29 mmol) was added portion-wise over a period of 5 minutes. After complete addition, the reaction mixture was allowed to stir at room temperature. After 6 hours, the reaction mixture was boiled for 10 minutes to expel the nitrous gases (visible as yellow fumes). The reaction mixture was then neutralized with sat. (aq) $NaHCO_3$ and extracted with ethyl acetate (25 mL). The ethyl acetate fraction was separated, washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The volatile components were then removed under vacuum and the residue purified by column chromatography on silica gel using Pet Ether:EtOAc (9:1 to 1:1) to afford the product **4a** (35 mg, 70 % yield) as a white solid, 70 % yield; M. p. 252-253 °C; R_f 0.19 (3:2 Pet Ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.67 (brs, 1H, NH), 7.48-7.37 (m, 4H, Ar-H), 7.34-7.26 (m, 6H, Ar-H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.1 (C), 146.7 (C), 133.4 (C), 130.2 (CH), 129.6 (CH), 128.8 (CH), 128.5 (CH), 127.9 (CH), 127.2 (CH), 126.6 (C) ppm; IR: $\tilde{\upsilon}$ (cm^{-1}) 3153, 3051, 2931, 1689, 1593, 1550, 1496, 1445, 1416, 1331; HRMS (ESI) calculated for $C_{14}H_{11}N_3NaO$ $[M+Na]^+$ 260.0794, found 260.0804.

3-anilino-2,4-diphenyl-1,2,4-triazole (286)



brown solid, M. p. 87-89 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ- 8.22-8.19 (m, 2H, Ar-H), 7.64-7.58 (m, 6H, Ar-H), 7.52-7.40 (m, 4H, Ar-H), 7.36 (t, *J* = 8.4 Hz, 2H, Ar-H), 7.06 (t, *J* = 7.48 Hz, 1H, Ar-H), 6.45 (brs, 1H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ- 159.4 (C), 150.7 (C), 138.9 (C), 136.3 (C), 130.7 (C), 130.1 (CH), 129.3 (CH), 129.2 (CH), 128.8 (CH), 128.4 (CH), 126.4 (CH), 124.6 (CH), 122.5 (CH), 117.7 (CH); IR ῡ (cm^{-1}): 2923, 2853, 1598, 1561, 1441; HRMS (ESI) calculated for $C_{20}H_{17}N_4$ $[M+H]^+$ 313.1448, found 313.1451.

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4.12 Crystallographic data

Table 4.1 Crystal data and structure refinement for 3,4-diphenyl-1,2,4-oxadiazol-5(4*H*)-one (**216**)

Identification code	pasjmb
Empirical formula	C14 H10 N2 O2
Formula weight	238.24
Temperature	120(2) K

Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 15.2095(12) Å	a= 90°.
	b = 5.9093(4) Å	b= 102.997(8)°.
	c = 12.9247(11) Å	g = 90°.
Volume	1131.86(16) $Å^3$	
Z	4	
Density (calculated)	1.398 Mg/m^3	
Absorption coefficient	0.784 mm^{-1}	
F(000)	496	
Crystal size	0.6815 x 0.5067 x 0.2868 mm^3	
Theta range for data collection	5.972 to 74.991°.	
Index ranges	-18<=h<=18, -7<=k<=7, -16<=l<=14	
Reflections collected	8812	
Independent reflections	2277 [R(int) = 0.0321]	
Completeness to theta = 67.684°	99.8 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.845 and 0.705	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2277 / 0 / 163	
Goodness-of-fit on F^2	1.026	
Final R indices [I>2sigma(I)]	R1 = 0.0433, wR2 = 0.1158	
R indices (all data)	R1 = 0.0464, wR2 = 0.1189	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.457 and -0.216 e.$Å^{-3}$	

Table 4.2 Crystal data and structure refinement for 2,4,5-Triphenyl-1*H*-1,2,4-triazol-3(4*H*)-imine (**285)**

Identification code	EN_SB_660P
Empirical formula	C20 H16 N4

Formula weight	312.37	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 19.1339(10) Å	a= 90°.
	b = 5.8057(3) Å	b= 112.9259(17)°.
	c = 15.2949(8) Å	g = 90°.
Volume	1564.84(14) $Å^3$	
Z	4	
Density (calculated)	1.326 Mg/m^3	
Absorption coefficient	0.639 mm^{-1}	
F(000)	656	
Crystal size	0.224 x 0.094 x 0.075 mm^3	
Theta range for data collection	2.507 to 72.356°.	
Index ranges	-21<=h<=23, -6<=k<=7, -18<=l<=18	
Reflections collected	20654	
Independent reflections	3081 [R(int) = 0.0640]	
Completeness to theta = 67.679°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7536 and 0.4278	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3081 / 0 / 220	
Goodness-of-fit on F^2	1.051	
Final R indices [I>2sigma(I)]	R1 = 0.0621, wR2 = 0.1610	
R indices (all data)	R1 = 0.0656, wR2 = 0.1660	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.366 and -0.382 $e.Å^{-3}$	

Table 4.3 Crystal data and structure refinement for **3-anilino-2,4-diphenyl-1,2,4-triazole (286)**

Identification code	cu_EN_SB_821_B_0m

Empirical formula	C20 H16 N4	
Formula weight	312.37	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.3202(2) Å	a= 90°.
	b = 11.7029(3) Å	b= 90°.
	c = 18.2850(5) Å	g = 90°.
Volume	1566.43(7) $Å^3$	
Z	4	
Density (calculated)	1.325 Mg/m^3	
Absorption coefficient	0.639 mm^{-1}	
F(000)	656	
Crystal size	0.267 x 0.147 x 0.089 mm^3	
Theta range for data collection	4.486 to 72.124°.	
Index ranges	-9<=h<=8, -14<=k<=14, -22<=l<=22	
Reflections collected	14411	
Independent reflections	3066 [R(int) = 0.0221]	
Completeness to theta = 67.679°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7536 and 0.6674	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3066 / 0 / 221	
Goodness-of-fit on F^2	1.089	
Final R indices [I>2sigma(I)]	R1 = 0.0258, wR2 = 0.0674	
R indices (all data)	R1 = 0.0262, wR2 = 0.0678	
Absolute structure parameter	0.08(9)	
Extinction coefficient	0.0031(4)	
Largest diff. peak and hole	0.194 and -0.136 $e.Å^{-3}$	

Table 4.4 Crystal data and structure refinement for 2,4,5-triphenyl-2*H*-1,2,4-triazol-3(4*H*)-one **(345)**

Identification code	EN_SB_796_P	
Empirical formula	C20 H15 N3 O	
Formula weight	313.35	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 19.0316(7) Å	a= 90°.
	b = 5.6528(2) Å	b= 111.7060(10)°.
	c = 15.3092(5) Å	g = 90°.
Volume	1530.21(9) $Å^3$	
Z	4	
Density (calculated)	1.360 Mg/m^3	
Absorption coefficient	0.688 mm^{-1}	
F(000)	656	
Crystal size	0.246 x 0.063 x 0.044 mm^3	
Theta range for data collection	2.499 to 72.174°.	
Index ranges	-23<=h<=23, -6<=k<=6, -18<=l<=18	
Reflections collected	26731	
Independent reflections	3002 [R(int) = 0.0261]	
Completeness to theta = 67.679°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7536 and 0.6592	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3002 / 0 / 217	
Goodness-of-fit on F^2	1.048	
Final R indices [I>2sigma(I)]	R1 = 0.0341, wR2 = 0.0856	
R indices (all data)	R1 = 0.0361, wR2 = 0.0874	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.195 and -0.277 $e.Å^{-3}$	